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☐	L17	5783186.pn.	2
☐	L16	L15 and p185neu	21
☐	L15	L14 and EGFR	2140
☐	L14	L13 and antibod?	19128
☐	L13	L12 and treatment	46051
☐	L12	psoriasis	55743
☐	L11	L10 and (p185neu)	28
☐	L10	(p185)same(antibod?)	277
☐	L9	(sliwkowski)adj(mark)adj(x)	41
☐	L8	(brunetta)adj(paul)adj(g)	24
☐	L7	L6 and ErbB2	8
☐	L6	L5 and antibody	81
☐	L5	(non-malignant)adj(disease)same(treatment)	156
☐	L4	L3 and anti-ErbB2	25
☐	L3	(ErbB2)same(psoriasis)	152
☐	L2	(treatment)same(psoriasis)same(ErbB2)adj(antibod?)	1
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                   fields
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=> s l2 and antibod?
L3 4105 L2 AND ANTIBOD?

=> s l3 and ErbB2
L4 5 L3 AND ERBB2

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L5 5 DUP REMOVE L4 (0 DUPLICATES REMOVED)

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L5 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN
2007:11341 Document No. 146:121941 Pyrrolo[2,3-b]pyridine derivatives as protein kinase inhibitors and their preparation, pharmaceutical compositions and use in the **treatment** of diseases. Ibrahim, Prabha N.; Artis, Dean R.; Bremer, Ryan; Habets, Gaston; Mamo, Shumeye; Nespi, Marika; Zhang, Chao; Zhang, Jiazhong; Zhu, Yong-Liang; Zuckerman, Rebecca; West, Brian; Suzuki, Yoshihisa; Tsai, James; Hirth, Klaus-Peter; Bollag, Gideon; Spevak, Wayne; Cho, Hanna; Gillette, Samuel J.; Wu, Guoxian; Zhu, Hongyao; Shi, Shenghua (Plexxikon, Inc., USA). PCT Int. Appl. WO 2007002433 A1 20070104, 631 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG,

PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2006-US24524 20060621. PRIORITY: US 2005-692960P 20050622; US 2005-731528P 20051028.

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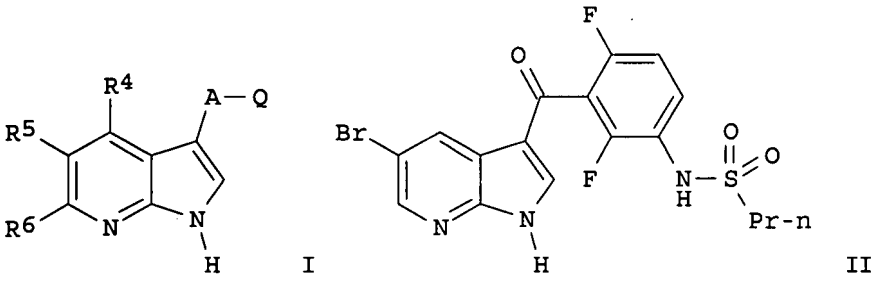

I II

AB Compds. of formula I which are active on protein kinases are described, as well as methods of using such compds. to **treat** diseases and conditions associated with aberrant activity of protein kinases. Compds. of formula I wherein Q is (un)substituted aryl, (un)substituted indole, (un)substituted heteroaryl, etc.; A is O, S, (un)substituted methylene, NH and derivs., CO, CS, SO and SO2; R4 - R6 is H, halo, (un)substituted lower alkyl, (un)substituted lower alkenyl, (un)substituted alkynyl, (un)substituted (hetero)cycloalkyl, and (un)substituted (hetero)aryl; and their pharmaceutically acceptable salts, prodrugs, tautomers, and isomers thereof, are claimed. Example compound II was prepared by carboxylation of 2,4-difluoroaniline with benzyl chloroformate; the resulting benzyl 3-amino-2,6-difluorobenzoate underwent sulfonylation with propane-1-sulfonyl chloride to give benzyl 2,6-difluoro-3-(propylsulfonylamino)benzoate, which underwent hydrogenation to give the corresponding benzoic acid, which underwent chlorination, to give the corresponding acid chloride, which underwent reaction with 5-bromo-7-azaindole to give compound II. All the invention compds. were evaluated for their protein kinase inhibitory activity. Several of the tested compds. exhibited good protein kinase inhibitory activity against several kinases.

L5 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN

2004:467984 Document No. 141:22217 Therapy of non-malignant diseases or disorders with anti-**ErbB2 antibodies.** Sliwkowski, Mark X.; Brunetta, Paul G. (Genentech, Inc., USA). PCT Int. Appl. WO 2004048525 A2 20040610, 74 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US37367 20031121. PRIORITY: US 2002-428027P 20021121.

AB The authors disclose the preparation and biol. activity of murine and humanized **antibodies** to HER2. In one example, an anti-HER2 **antibody** is shown to inhibit heregulin-induced activation of Akt kinase and **erbB2** association with erbB3. The present application describes **treatment** of non-malignant indications, such as **psoriasis**, endometriosis, scleroderma, vascular diseases or disorders, respiratory

disease, colon polyps or fibroadenoma, with anti-**ErbB2** **antibodies** (e.g. rhuMAb 2C4).

L5 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN
2004:200102 Document No. 140:235750 Preparation of quinazolines as epidermal growth factor receptor (erbB) inhibitors for the **treatment** of proliferative diseases. Kath, John Charles; Tom, Norma Jacqueline; Cox, Eric David; Bhattacharya, Samit Kumar (Pfizer Products Inc., USA). Eur. Pat. Appl. EP 1396489 A1 20040310, 26 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY. (English). CODEN: EPXXDW. APPLICATION: EP 2003-24331 19991224. PRIORITY: US 1999-117341P 19990127; EP 1999-310574 19991224.

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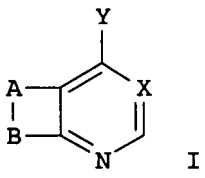

I

AB Title compds. I [X = N, CH; A-B = R4-substituted fused pyridyl, pyrimidyl, furanyl, etc.; Y = NR1R3; R1, R2 = H, alkyl; R3 = -(CR1R2)m-R8 or R1 and R3 are taken together with N; R4 = -(CR1R2)p-aryl, -(CR1R2)p-heterocyclic, -(CR1R2)q-NR1R9, etc.; R8 = -(CR1R2)p-aryl, -(CR1R2)p-heterocyclic; R9 = fused or bridged bicyclic ring, spirocyclic ring with provisos; m= 0, 1; p, q = 0-5] and their pharmaceutically acceptable salts were prepared For example, coupling of compound I [X = N; A-B = -CR4=CH-CH=CH-; Y = OPh; R4 = 4-((6-hydroxymethyl-3-aza-bicyclo[3.1.0]hex-3-yl)methyl)phenyl], e.g., prepared from 6-iodo-4-quinazolinone in 4-steps, with 1-cyclopropylmethyl-1H-indol-5-ylamine, afforded compound I [X = N; A-B = -CR4=CH-CH=CH-; Y = 1-cyclopropylmethyl-1H-indol-5-ylamino; R4 = 4-((6-hydroxymethyl-3-aza-bicyclo[3.1.0]hex-3-yl)methyl)phenyl] in 67% yield. In c-**erbB2** kinase inhibition assays, compds. I showed potent (sic.) inhibition of the **erbB2** tyrosine kinase activity (no data provided). Compds. I are claimed useful for the **treatment** of cancer and benign proliferative diseases, e.g., **psoriasis.**

L5 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN
2001:380440 Document No. 135:18554 Targeted delivery of therapeutic and diagnostic moieties. Press, Michael; Park, Jinha (University of Southern California, USA). PCT Int. Appl. WO 2001036005 A2 20010525, 66 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US31424 20001115. PRIORITY: US 1999-PV165563 19991115.

AB Compns. and methods for improving cellular internalization of one or more compds. are disclosed. The invention provides a drug conjugate composition that can be delivered to a target cell, which comprises a carrier compound that has a binding specificity for a receptor mol. and is conjugated to a therapeutic or diagnostic moiety. When this composition is administered to a subject, the carrier compound binds to the receptor and is internalized by the target cell. Furthermore, monoclonal **antibodies** are disclosed that are internalized into target cells. The monoclonal **antibodies** of the invention are specific for target cells, particularly for cells expressing the surface antigen p185HER-2. The **antibodies** of the invention may be conjugated with a mol. for

delivery into a target cell. Such mols. may be used for therapeutic **treatment**, including gene therapy, and for imaging. The invention also provides DNA sequences of the variable regions of particular monoclonal **antibodies.**

L5 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN
2000:210344 Document No. 132:247117 Cell proliferative disease diagnosis method by cytosine methylation analysis in cytokine receptor gene. Homma, Yoshimi; Oyama, Noritaka; Sato, Koichiro (Kyowa Hakko Kogyo Co., Ltd., Japan). PCT Int. Appl. WO 2000017339 A1 20000330, 31 pp. DESIGNATED STATES: W: AU, BG, BR, CA, CN, CZ, HU, ID, IL, IN, JP, KR, MX, NO, NZ, PL, RO, SG, SI, SK, UA, US, VN, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1999-JP5069 19990917. PRIORITY: JP 1998-265089 19980918.
AB Methods for the diagnosis of a cell proliferative disease characterized by analyzing the extent of the methylation of cytosine residues in a region associated with the expression of a cytokine receptor gene are disclosed. **Psoriasis** was diagnosed by analyzing the extent of CpG island cytosine residues in the promoter region of epidermal growth factor receptor (EGF-R) gene via sodium sulfite **treatment** and PCR amplification. Chronic rheumatoid arthritis was similarly diagnosed by analyzing the extent of CpG island cytosine residues in the promoter region of epidermal growth factor receptor 2 (**erbB2**/HER2/neu) gene.

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L6 10 L3 AND HER2

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L7 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN
2006:99983 Document No. 144:184708 Use of K-252a and kinase inhibitors for the prevention or **treatment** of HMGB1-associated pathologies. Fumero, Silvano; Pilato, Francesco, P.; Barone, Domenico; Bertarione, Rava, Rossa, Luisa; Mainero, Valentina; Traversa, Silvio (Creabilis Therapeutics S.p.A., Italy; Bio3research Srl). PCT Int. Appl. WO 2006010628 A1 20060202, 63 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-EP8258 20050729. PRIORITY: US 2004-591880P 20040729; US 2005-647007P 20050127.
AB The present invention relates to the use of K-252a, a physiol. active substance produced by microorganisms, and/or a kinase inhibitor and of its salts or synthetic and/or chemical modified derivs. for the prevention or **treatment** of HMGB1-associated pathologies. More particularly, the present invention relates to the use of K-252a for the prevention or **treatment** of restenosis.

L7 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN
2006:53052 Document No. 144:150398 Preparation of pyrrolotriazines with ability to inhibit tyrosine kinase activity of growth factor receptors. Gavai, Ashvinikumar, V.; Mastalerz, Harold; Daris, Jean-Paul; Dextraze, Pierre; Lapointe, Philippe; Ruediger, Edward, H.; Vyas, Dolatrai, M.; Zhang, Guifen (Bristol-Myers Squibb Company, USA). PCT Int. Appl. WO

2006007468 A1 20060119, 79 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-US22059 20050622. PRIORITY: US 2004-584768P 20040701.

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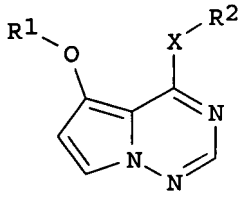

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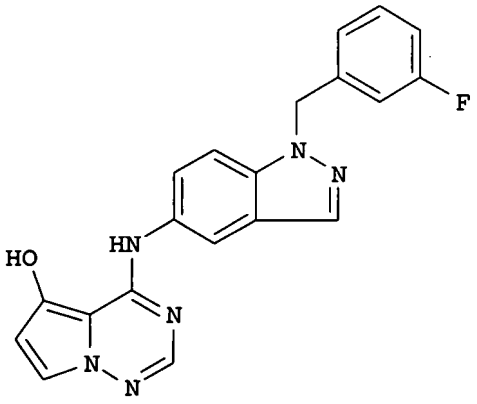

II

AB Title compds. I [R1 = H, (un)substituted alkyl, cycloalkyl, etc.; R2 = (un)substituted aryl or heterocyclyl; X = bond or NH], and their pharmaceutically acceptable salts, are prepared and disclosed as having the ability to inhibit tyrosine kinase activity of growth factor receptors such as HER1, **HER2** and HER4 thereby making them useful as antiproliferative agents. Thus, e.g., II was prepared by oxidation of (4-(1-(3-fluorobenzyl)-1H-indazol-5-ylamino)pyrrolo[1,2-f][1,2,4]triazin-5-yl)methanol to the corresponding formaldehyde derivative which is oxidatively decarboxylated. I demonstrated IC50 values between 0.001 and 25 μM when assayed against HER1, **HER2** and HER4 kinases. The compds. are also useful for the **treatment** of other diseases associated with signal transduction pathways operating through growth factor receptors.

L7 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN

2006:1012656 Document No. 145:377380 Aminoquinazoline derivatives as ATP competitive kinase inhibitors and their preparation, pharmaceutical composition, useful as antiproliferative agents. Gavai, Ashvinikumar V.; Chen, Ping; Zhao, Yufen (USA). U.S. Pat. Appl. Publ. US 2006217369 A1 20060928, 24pp. (English). CODEN: USXXCO. APPLICATION: US 2006-389797 20060327. PRIORITY: US 2005-665826P 20050328.

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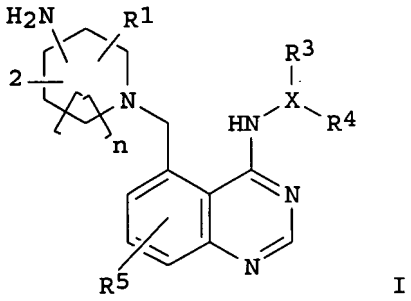

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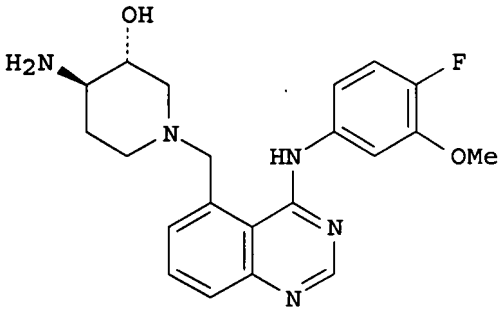

II

AB The invention provides compds. of formula I and pharmaceutically acceptable salts thereof. The formula I compds. inhibit tyrosine kinase activity of growth factor receptors such as HER1, **HER2** and HER4 thereby making them useful as antiproliferative agents. The formula I compds. are also useful for the **treatment** of other diseases associated with signal transduction pathways operating through growth factor receptors. Compds. of formula II wherein R1 and R2 are independently H, halo, OH, (un)substituted alkyl, CN, NH2, CONHR3, OCONHR3, CONHSO2R3, etc.; R3 is H and C1-4 alkyl, R4 is (un)substituted (hetero)aryl, etc.; R5 is halo and C1-6 alkyl(oxy); X is bond and CH; n is 0, 1, and 2; and their pharmaceutically acceptable salts and stereoisomers are claimed. Example compound II was prepared by cyclization of 2-amino-6-methylbenzoic acid with formamide; the resulting 5-methylquinazolin-4(3H)-one underwent chlorination to give 4-chloro-5-methylquinazoline, which underwent substitution to give 5-methyl-4-(methylthio)quinazoline, which underwent bromination followed by amination with (3R,4R)-4-azidopiperidin-3-ol to give (3R,4R)-4-azido-1-((4-(methylthio)quinazolin-5-yl)methyl)piperidin-3-ol, which underwent substitution with 4-fluoro-3-methoxyaniline followed by reduction to give compound II. All the invention compds. were evaluated for their ATP competitive kinase inhibitory activity. The tested compds. exhibited IC50 values in the range of 0.001 to 25 μM. The most active compds. showed IC50 values in the range of 0.001 to 0.1 μM.

L7 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN

2006:388494 Document No. 144:432842 Preparation of pyrrolotriazines useful as antiproliferative agents and for **treatment** of other diseases-assocd. with signaling pathways operating through growth factor receptors. Gavai, Ashvinikumar V.; Han, Wen-Ching; Zhao, Yufen; Chen, Ping (Bristol-Myers Squibb Company, USA). U.S. Pat. Appl. Publ. US 2006089358 A1 20060427, 18 pp. (English). CODEN: USXXCO. APPLICATION: US 2005-253832 20051019. PRIORITY: US 2004-620784P 20041021.

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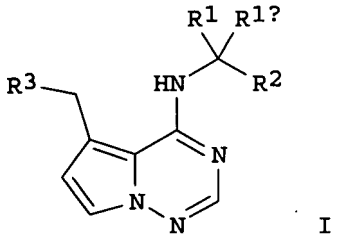

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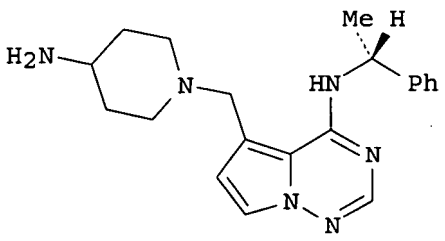


II

AB The title compds. I [R1, R1a = H, alkyl, Ph; R2 = (un)substituted (hetero)aryl; R3 = (un)substituted heterocyclyl] which inhibit tyrosine kinase activity of growth factor receptors such as HER1, **HER2** and HER4 thereby making them useful as antiproliferative agents, were prepared E.g., a multi-step synthesis of (1R)-II, starting from 5-(bromomethyl)-4-chloropyrrolo[1,2-f][1,2,4]triazine, was given. Compds. I were tested in HER1, **HER2** or HER4 kinase assays. The instant compds. inhibit HER1, **HER2**, and HER4 kinases with IC50 values between 0.001 and 25 μM. The compds. I are also useful for the **treatment** of other diseases associated with signal transduction pathways operating through growth factor receptors.

L7 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN

2005:490384 Document No. 143:42681 Anti-IGFR-1 **antibodies** in combination with chemotherapeutic agent for **treating** cancer. Wang, Yan; Pachter, Jonathan A.; Bishop, Walter R. (Schering Corporation, USA). PCT Int. Appl. WO 2005052005 A1 20050609, 97 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US38842 20041119. PRIORITY: US 2003-524732P 20031121.

AB The present invention provides combinations including a binding composition, such as an anti-IGFR1 **antibody**, in association with a chemotherapeutic agent. The **antibody** is e.g. a human monoclonal **antibody** recognizing human IGFR-1, especially soluble IGFR-1. The chemotherapeutic agent is selected from a taxane, topoisomerase inhibitor, signal transduction inhibitor, cell cycle inhibitor, farnesyl protein transferase inhibitor, EGFR inhibitor, **HER2** inhibitor, VEGFR inhibitor, MAP kinase inhibitor, MEK kinase inhibitor, AKT kinase inhibitor, mTOR inhibitor, etc. Methods for using the combinations to **treat** medical conditions, such as cancer, are also provided.

L7 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN

2004:965067 Document No. 141:406039 Combinations for the **treatment** of diseases involving cell proliferation, migration or apoptosis of myeloma cells, or angiogenesis. Hilberg, Frank; Solca, Flavio; Stefanic, Martin Friedrich; Baum, Anke; Munzert, Gerd; Van Meel, Jacobus C. A. (Boehringer Ingelheim International G.m.b.H., Germany; Boehringer Ingelheim Pharma G.m.b.H. & Co. K.-G.). PCT Int. Appl. WO 2004096224 A2 20041111, 101 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN:

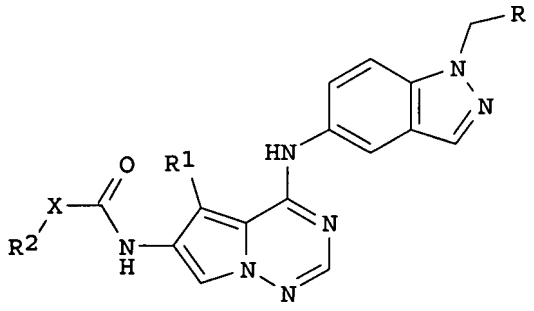
PIXXD2. APPLICATION: WO 2004-EP4363 20040424. PRIORITY: EP 2003-9587 20030429; EP 2004-508 20040113; EP 2004-1171 20040121.

AB The present invention relates to a pharmaceutical combination for the **treatment** of diseases which involves cell proliferation, migration or apoptosis of myeloma cells, or angiogenesis. The invention also relates to a method for the **treatment** of said diseases, comprising co-administration of effective amts. of specific active compds. and/or co-**treatment** with radiation therapy, in a ratio which provides an additive and synergistic effect, and to the combined use of these specific compds. and/or radiotherapy for the manufacture of corresponding pharmaceutical combination prepns. The pharmaceutical combination can include selected protein tyrosine kinase receptor antagonists and further chemotherapeutic or naturally occurring semisynthetic or synthetic agents.

L7 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN

2004:531311 Document No. 141:89122 Preparation of C-6 modified indazolyl pyrrolotriazines as antiproliferative agents. Vite, Gregory D.; Gavai, Ashvinikumar V.; Fink, Brian E.; Mastalerz, Harold; Kadow, John F. (Bristol-Myers Squibb Company, USA). PCT Int. Appl. WO 2004054514 A2 20040701, 81 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US39542 20031212. PRIORITY: US 2002-433190P 20021213.

GI



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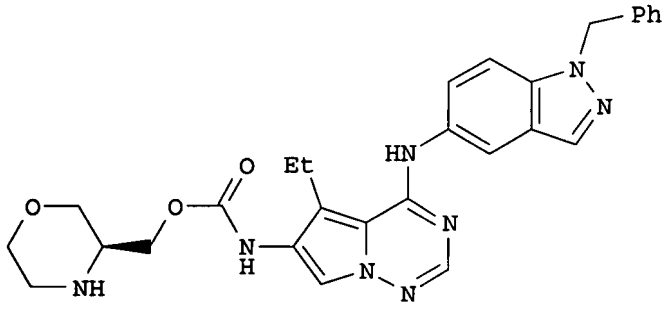


II

AB The title compds. [I; R = (un)substituted aryl, heterocyclyl; R1 = (un)substituted alkyl; R2 = H, (un)substituted alkyl, cycloalkyl, aryl, etc.; X = a bond, O, S, (un)substituted NH, etc.] and their pharmaceutically acceptable salts which inhibit tyrosine kinase activity

of growth factor receptors such as HER1, **HER2** and HER4 thereby making them useful as antiproliferative agents, were prepared E.g., a multi-step synthesis of (3S)-II.HCl, starting from 5-nitroindazole, was given. Preferred compds. I exhibit IC50 of < 5 μM in one or more of HER1, **HER2** and HER4 assays. The compds. I are also useful for the **treatment** of other diseases associated with signal transduction pathways operating through growth factor receptors. The pharmaceutical composition comprising the compound I is claimed.

L7 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN

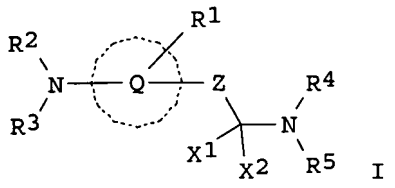
2004:467984 Document No. 141:22217 Therapy of non-malignant diseases or disorders with anti-ErbB2 **antibodies.** Sliwkowski, Mark X.; Brunetta, Paul G. (Genentech, Inc., USA). PCT Int. Appl. WO 2004048525 A2 20040610, 74 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US37367 20031121. PRIORITY: US 2002-428027P 20021121.

AB The authors disclose the preparation and biol. activity of murine and humanized **antibodies** to **HER2.** In one example, an anti-**HER2 antibody** is shown to inhibit heregulin-induced activation of Akt kinase and erbB2 association with erbB3. The present application describes **treatment** of non-malignant indications, such as **psoriasis**, endometriosis, scleroderma, vascular diseases or disorders, respiratory disease, colon polyps or fibroadenoma, with anti-ErbB2 **antibodies** (e.g. rhuMAb 2C4).

L7 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN

2004:220082 Document No. 140:253556 Preparation of 5-thiazolecarboxamides as protein tyrosine kinase inhibitors. Das, Jagabandhu; Padmanabha, Ramesh; Chen, Ping; Norris, Derek J.; Doweyko, Arthur M. P.; Barrish, Joel C.; Wityak, John; Lombardo, Louis J.; Lee, Francis Y. F. (Bristol-Myers Squibb Company, USA). U.S. Pat. Appl. Publ. US 2004054186 A1 20040318, 184 pp., Cont.-in-part of U.S. 6,596,746. (English). CODEN: USXXCO. APPLICATION: US 2003-395503 20030324. PRIORITY: US 2000-548929 20000413; US 1999-129510P 19990415.

GI



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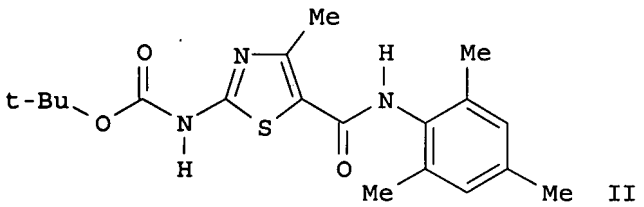

II

AB The title compds. [I; Q = (un)substituted 5-6 membered heteroaryl, aryl; Z = a single bond, R15C:CH, (CH2)m (m = 1-2); X1, X2 = H; X1 and X2 together = O, S; R1 = H, alkyl, alkenyl, etc.; R2, R3 = H, alkyl, alkenyl, etc.; R4, R5 = H, alkyl, alkenyl, etc.], useful in the **treatment** of protein tyrosine kinase-associated disorders such as immunol. and oncol. disorders (no data), were prepared E.g., a multi-step synthesis of thiazole II was given. Compds. I are effective at 0.1-100 mg/kg/day. The pharmaceutical composition comprising the title compds. is claimed.

L7 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN
2000:210344 Document No. 132:247117 Cell proliferative disease diagnosis method by cytosine methylation analysis in cytokine receptor gene. Homma, Yoshimi; Oyama, Noritaka; Sato, Koichiro (Kyowa Hakko Kogyo Co., Ltd., Japan). PCT Int. Appl. WO 2000017339 A1 20000330, 31 pp. DESIGNATED STATES: W: AU, BG, BR, CA, CN, CZ, HU, ID, IL, IN, JP, KR, MX, NO, NZ, PL, RO, SG, SI, SK, UA, US, VN, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1999-JP5069 19990917. PRIORITY: JP 1998-265089 19980918.
AB Methods for the diagnosis of a cell proliferative disease characterized by analyzing the extent of the methylation of cytosine residues in a region associated with the expression of a cytokine receptor gene are disclosed. **Psoriasis** was diagnosed by analyzing the extent of CpG island cytosine residues in the promoter region of epidermal growth factor receptor (EGF-R) gene via sodium sulfite **treatment** and PCR amplification. Chronic rheumatoid arthritis was similarly diagnosed by analyzing the extent of CpG island cytosine residues in the promoter region of epidermal growth factor receptor 2 (erbB2/**HER2**/neu) gene.

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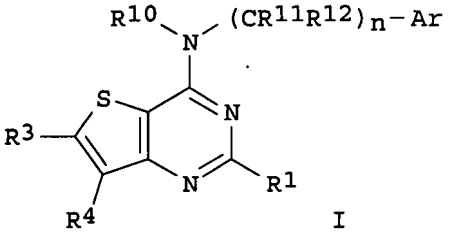
L12 ANSWER 1 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN
2007:484377 Document No. 146:482086 Preparation of N-arylalkyl-thienopyrimidin-4-amines and analogs as activators of caspases and inducers of apoptosis. Cai, Sui Xiong; Drewe, John A.; Kemnitzer, William E.; Sirisoma, Nilantha Sudath (Cytovia, Inc., USA). U.S. Pat. Appl. Publ. US 2007099941 A1 20070503, 23pp. (English). CODEN: USXXCO. APPLICATION: US 2006-591531 20061102. PRIORITY: US 2005-732139P 20051102.
GI



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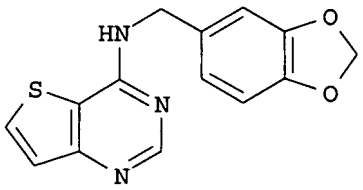
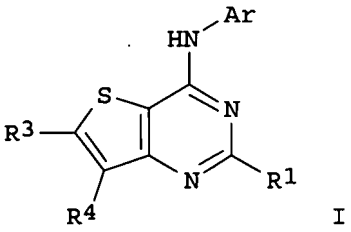


II

AB Disclosed are N-arylalkyl-thienopyrimidin-4-amines and analogs thereof, represented by the formula I [wherein Ar =(un)substituted (hetero)aryl; R1 = H, halo, (un)substituted amino, etc.; R3, R4 = independently H, halo, alkyl, etc.; R10 = H or (un)substituted alkyl; R11, R12 = independently H or (un)substituted alkyl; n = 1-3; and pharmaceutically acceptable salts prodrugs or tautomers thereof] were prepared as activators of caspases and inducers of apoptosis. For example, reaction of 4-chlorothieno[3,2-d]pyrimidine with 3,4-methylenedioxybenzylamine gave II in 43% yield. I were identified as Caspase Cascade activators and inducers of Apoptosis in human breast cancer cell line T-47D and human lung cancer cell line H1299, and as antineoplastic agents. Therefore, the activators of caspases and inducers of apoptosis of this invention may be used to induce cell death in a variety of clin. conditions in which uncontrolled growth and spread of abnormal cells occurs.

L12 ANSWER 2 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN
2007:484293 Document No. 146:482085 Preparation of N-aryl-thienopyrimidin-4-amines and analogs as activators of caspases and inducers of apoptosis. Cai, Sui Xiong; Kemnitzer, William E.; Sirisoma, Nilantha Sudath; Zhang, Han-Zhong (Cytovia, Inc., USA). U.S. Pat. Appl. Publ. US 2007099877 A1 20070503, 34pp. (English). CODEN: USXXCO. APPLICATION: US 2006-591532 20061102. PRIORITY: US 2005-732140P 20051102.

GI



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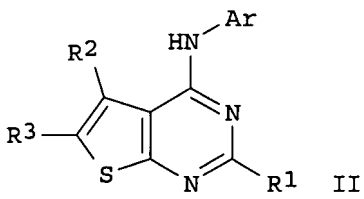


II

AB Disclosed are N-aryl-thienopyrimidin-4-amines and analogs thereof, represented by the formula I & II [wherein Ar =(un)substituted (hetero)aryl; R1 = H, halo, (un)substituted amino, etc.; R2-R4 = independently H, halo, alkyl, etc.] and pharmaceutically acceptable salts prodrugs or tautomers thereof. For example, reaction of 4-chloro-2-methylthieno[3,2-d]pyrimidine with 2,5-dimethoxyaniline gave N-(2,5-dimethoxyphenyl)-2-methylthieno[3,2-d]pyrimidin-4-amine in 51% yield. I were identified as Caspase Cascade activators and inducers of Apoptosis in human breast cancer cell line T-47D and human lung cancer cell line H1299, and as antineoplastic agents. Therefore, the activators of caspases and inducers of apoptosis of this invention may be used to induce cell death in a variety of clin. conditions in which uncontrolled growth and spread of abnormal cells occurs.

L12 ANSWER 3 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
2007105905 EMBASE Recombinant therapeutic antibodies. Dubel S.. S. Dubel,

Technical University of Braunschweig, Institute of Biochemistry and Biotechnology, Spielmannstr. 7, Braunschweig 38106, Germany. s.duebel@tu-bs.de. Applied Microbiology and Biotechnology Vol. 74, No. 4, pp. 723-729 2007.
Refs: 24.
ISSN: 0175-7598. CODEN: AMBIDG
Pub. Country: Germany. Language: English. Summary Language: English.
Entered STN: 20070322. Last Updated on STN: 20070322

AB Recombinant antibody technology has revolutionized the development of antibody therapeutics. This minireview offers an overview of enabling technologies and future prospects of this rapidly progressing field. .COPYRGT. 2007 Springer-Verlag.

L12 ANSWER 4 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2007125866 EMBASE Immunogenicity screening in protein drug development. Van Walle I.; Gansemans Y.; Parren P.W.H.I.; Stas P.; Lasters I.. I. Van Walle, Algonomics NV, Technologiepark 4, 9052 Gent-Zwijnaarde, Belgium. ivo.van.walle@algonomics.com. Expert Opinion on Biological Therapy Vol. 7, No. 3, pp. 405-418 2007.
Refs: 113.
ISSN: 1471-2598. CODEN: EOBTA2
Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 20070403. Last Updated on STN: 20070403

AB Most therapeutic proteins in clinical trials or on the market are, to a variable extent, immunogenic. Formation of antidrug antibodies poses a risk that should be assessed during drug development, as it possibly compromises drug safety and alters pharmacokinetics. The generation of these antibodies is critically dependent on the presence of T helper cell epitopes, which have classically been identified by in vitro methods using blood cells from human donors. As a novel development, in silico methods that identify T cell epitopes have been coming on line. These methods are relatively inexpensive and allow the mapping of epitopes from virtually all human leukocyte antigen molecules derived from a wide genetic background. In vitro assays remain important, but guided by in silico data they can focus on selected peptides and human leukocyte antigen haplotypes, thereby significantly reducing time and cost. .COPYRGT. 2007 Informa UK Ltd.

L12 ANSWER 5 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2007118983 EMBASE Tyrosine kinases as targets for anti-inflammatory therapy. Tamura T.; Koch A.. A. Koch, Institut fur Biochemie, Medizinische Hochschule Hannover, Carl-Neuberg-Str. 1, D-30623 Hannover, Germany. koch.alexandra@mh-hannover.de. Anti-Inflammatory and Anti-Allergy Agents in Medicinal Chemistry Vol. 6, No. 1, pp. 47-60 2007.
Refs: 191.
ISSN: 1871-5230. Pub. Country: Netherlands. Language: English. Summary Language: English.
Entered STN: 20070402. Last Updated on STN: 20070402

AB Tyrosine kinases play key roles in cell proliferation, differentiation, survival, cell migration, tissue development, and cell metabolisms. Mutation and/or truncation in tyrosine kinases result in their constitutive activation independent of ligand stimulation. The constitutively activated tyrosine kinase often triggers cancer development. Furthermore, it is well documented that overexpression of tyrosine kinases is involved in malignancy. In inflammatory lesion, tyrosine kinases are also activated via over-production of growth factors and/or cytokines from tissues. Several recent studies have demonstrated that targeting tyrosine kinases in inflammatory disease may lead to an useful therapy. In this review, we describe tyrosine kinases that are or may be involved in inflammatory disease such as stem cell factor (SCF) receptor (c-Kit), platelet derived growth factor (PDGF) receptors, macrophage colony stimulating factor (M-CSF) receptor (c-Fms), Trk

receptors, vascular endothelial growth factor (VEGF) receptors, fibroblast growth factor (FGF) receptors, epidermal growth factor (EGF) receptors, macrophage stimulating protein receptor (Ron), Janus kinases (Jak), and spleen tyrosine kinase (Syk)/zeta-chain associated protein kinase of 70 kDa (ZAP-70). In addition we describe potential tools and methods that can be applied for therapy, such as small molecule kinase inhibitors, antibodies, small peptides, or truncated receptors. Since inflammatory diseases are generally complex host reactions for a long term, and tyrosine kinases are important for maintenance of cell homeostasis, a successful tyrosine kinase targeting therapy will require many further studies. .COPYRGT. 2007 Bentham Science Publishers Ltd.

L12 ANSWER 6 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2007048343 EMBASE Biologic therapies: What and when?. Johnston S.L.. S.L. Johnston, Department of Immunology and Immunogenetics, Southmead Hospital, Westbury-on-Trym, Bristol BS10 5NB, United Kingdom. sarah.johnston@nbt.nhs.uk. Journal of Clinical Pathology Vol. 60, No. 1, pp. 8-17 2007.
Refs: 55.
ISSN: 0021-9746. CODEN: JCPAAK
Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 20070227. Last Updated on STN: 20070227

AB Over the past two decades, major advances have been made in the understanding of the immune system and disease pathogenesis. This has coincided with the development of biologic therapies-monoclonal antibodies and fusion proteins. The decision of when to use such treatment in the clinic is not always straightforward. In addition to immune biology, the focus of this review will be on the application of these treatments to immune-mediated diseases and the molecular targets involved in pathogenesis, specifically those that have US Food and Drug Administration/European Medicines Agency approval. Brief comments will be made on biologics that have approval for non-immune disorders.

L12 ANSWER 7 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2007125385 EMBASE Monoclonal antibodies: Pharmacological relevance. Kaur J.; Badyal D.K.; Khosla P.P.. J. Kaur, Department of Pharmacology, Christian Medical College and Hospital, Ludhiana, India. narulajasleen@yahoo.com. Indian Journal of Pharmacology Vol. 39, No. 1, pp. 5-14 1 Jan 2007.
Refs: 79.
ISSN: 0253-7613. CODEN: INJPD2
Pub. Country: India. Language: English. Summary Language: English.
Entered STN: 20070403. Last Updated on STN: 20070403

AB Monoclonal antibodies (MAbs), a new class of biological agents, are used these days in therapeutics and diagnosis. MAbs also labeled as 'magic bullets', are highly specific antibodies produced by a clone of single hybrid cells formed in the laboratory by fusion of B cell with the tumor cell. The hybridoma formed yields higher amount of MAbs. MAbs can be produced in vitro and in vivo. Animals are utilized to produce MAbs, but these antibodies are associated with immunogenic and ethical problems. Of late, recombinant DNA technology, genetic engineering,phage display and transgenic animals are used to produce humanized MAbs or pure human MAbs, which have fewer adverse effects. MAbs alone or conjugated with drugs, toxins, or radioactive atoms are used for treatment of cancer, autoimmune disorders, graft rejections, infectious diseases, asthma, and various cardiovascular disorders. New MAbs are being developed which are more specific and less toxic.

L12 ANSWER 8 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2007029167 EMBASE Antibody structure, instability, and formulation. Wang W.; Singh S.; Zeng D.L.; King K.; Nema S.. W. Wang, Pfizer, Inc., Global Biologics, 700 Chesterfield Parkway West, Chesterfield, MO 63017, United

States. wei.2.wang@pfizer.com. Journal of Pharmaceutical Sciences Vol. 96, No. 1, pp. 1-26 2007.
Refs: 115.
ISSN: 0022-3549. E-ISSN: 1520-6017. CODEN: JPMSAE
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20070226. Last Updated on STN: 20070226

AB The number of therapeutic monoclonal antibody in development has increased tremendously over the last several years and this trend continues. At present there are more than 23 approved antibodies on the US market and an estimated 200 or more are in development. Although antibodies share certain structural similarities, development of commercially viable antibody pharmaceuticals has not been straightforward because of their unique and somewhat unpredictable solution behavior. This article reviews the structure and function of antibodies and the mechanisms of physical and chemical instabilities. Various aspects of formulation development have been examined to identify the critical attributes for the stabilization of antibodies. .COPYRGT. 2006 Wiley-Liss, Inc.

L12 ANSWER 9 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN

2006:845649 Document No. 145:270004 Identification and engineering of antibodies with variant Fc regions. Stavenhagen, Jeffrey; Vijh, Sujata; Rankin, Christopher; Gorlatov, Sergey; Huang, Ling (Macrogenics, Inc., USA). PCT Int. Appl. WO 2006088494 A2 20060824, 325pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-US24645 20050712. PRIORITY: US 2004-587251P 20040712; US 2004-902588 20040728.

AB The authors disclose the engineering of the Fc region of antibodies wherein the resulting variant Fc regions comprise at least one amino acid modification relative to a wild-type Fc region and bind FcγRIIIA and/or FcγRIIA with a greater affinity. In one example, yeast display of mutant human Fc fragments was used to select for variants exhibiting increased binding to soluble FcγRIIIA tetramers. Fused to the variable region of an anti-fluorescein antibody, the chimeric antibody exhibited an enhanced ADCC effector function. The Fc variants are particularly useful for the treatment or prevention of a disease or disorder where an enhanced efficacy of effector cell function (e.g., ADCC) mediated by FcγR is desired, e.g., cancer, infectious disease, and in enhancing the therapeutic efficacy of therapeutic antibodies the effect of which is mediated by ADCC.

L12 ANSWER 10 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN

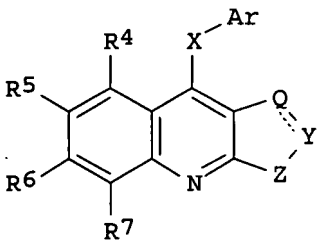
2006:515900 Document No. 145:1037 Method and composition using agents increasing intracellular accumulation of NADH + H+ for enhancing anti-angiogenic therapy. Ben-Sasson, Shmuel A. (Yissum Research Development Company of the Hebrew University of Jerusalem, Israel). PCT Int. Appl. WO 2006056889 A2 20060601, 32 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-IB4069 20051005. PRIORITY: US 2004-616348P 20041006.

AB The invention relates to the discovery that agents that increase intracellular accumulation of NADH + H+ enhance the anticancer effects of angiogenesis inhibitors. Furthermore, treatment of a mammal with a

combination of at least one angiogenesis inhibitor and at least one agent that enhances intracellular accumulation of NADH + H+ allows for the enhanced treatment and/or prevention of angiogenic diseases and disorders.

L12 ANSWER 11 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN
2006:366977 Document No. 144:412498 Preparation of substituted N-aryl-1H-pyrazolo[3,4-b]quinolin-4-amines and analogs as activators of caspases and inducers of apoptosis. Zhang, Han-Zhong; Cai, Sui Xiong; Drewe, John A. (Cytovia, Inc., USA). PCT Int. Appl. WO 2006041900 A2 20060420, 79 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-US35793 20051006. PRIORITY: US 2004-616539P 20041007.

GI

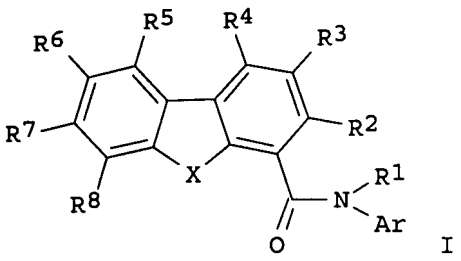


I

AB The title compds. I [X = O, NR3, S, SO, SO2; Ar = (un)substituted aryl, heteroaryl, carbocyclyl, etc.; Q = CR2, CR12R13; Y = N, CR10R11; Z = NR1, CR8R9; R1, R3 = H, (un)substituted alkyl; R2, R4-R13 = H, halo, aryl, etc.] which are activators of caspases and inducers of apoptosis and therefore can be used to induce cell death in a variety of clin. conditions in which uncontrolled growth and spread of abnormal cells occurs (biol. data given), were prepared E.g., a multi-step synthesis of 1,3-dimethyl-N-[4-(methoxycarbonyl)phenyl]-1H-pyrazolo[3,4-b]quinolin-4-amine, starting from anthranilic acid and 4-methyleneoxetan-2-one, was given. Pharmaceutical composition comprising the compound I alone or in combination with other therapeutic agents are disclosed.

L12 ANSWER 12 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN
2006:343269 Document No. 144:390567 Preparation of N-aryl-9-oxo-9H-fluorene-1-carboxamides and analogs as activators of caspases and inducers of apoptosis.. Kemnitzer, William E.; Cai, Sui Xiong; Drewe, John A.; Sirisoma, Nilantha Sudath (Cytovia, Inc., USA). PCT Int. Appl. WO 2006039356 A2 20060413, 79 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-US34890 20050929. PRIORITY: US 2004-613817P 20040929.

GI



I

AB Title compds. [I; X = CR9RR10, O, NR9, S, CO, SO, SO2; Ar = (substituted) aryl, heteroaryl, carbocyclyl, heterocyclyl, aralkyl, heteroaralkyl; R1 = H, (substituted) alkyl; R2-R8 = H, halo, haloalkyl, (substituted) fused aryl, heteroaryl, carbocyclyl, heterocyclyl, NO2, amino, cyano, etc.; R9, R10 = H, OH, (substituted) alkyl], were prepared Thus, N-(2-azidophenyl)-9-oxo-9H-fluorene-1-carboxamide (preparation via diazotization of the corresponding amine given) inhibited proliferation of T-47D cells with GI50 = 45 nM.

L12 ANSWER 13 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2006550122 EMBASE Non-fucosylated therapeutic antibodies as next-generation therapeutic antibodies. Satoh M.; Iida S.; Shitara K.. M. Satoh, Kyowa Hakko Kogyo Co. Ltd., Tokyo Research Laboratories, 3-6-6 Asahi-machi, Machida-shi, Tokyo 194-8533, Japan. msatoh@kyowa.co.jp. Expert Opinion on Biological Therapy Vol. 6, No. 11, pp. 1161-1173 2006.
Refs: 112.
ISSN: 1471-2598. CODEN: EOBTA2
Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 20061123. Last Updated on STN: 20061123

AB Most of the existing therapeutic antibodies that have been licensed and developed as medical agents are of the human IgG1 isotype, the molecular weight of which is .apprx.150 kDa. Human IgG1 is a glycoprotein bearing two N-linked biantennary complex-type oligosaccharides bound to the antibody constant region (Fc), in which the majority of the oligosaccharides are core fucosylated, and it exercises the effector functions of antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity through the interaction of the Fc with either leukocyte receptors (FcγRs) or complement. Recently, therapeutic antibodies have been shown to improve overall survival as well as time to disease progression in a variety of human malignancies, such as breast, colon and haematological cancers, and genetic analysis of FcγR polymorphisms of cancer patients has demonstrated that ADCC is a major antineoplasm mechanism responsible for clinical efficacy. However, the ADCC of existing licensed therapeutic antibodies has been found to be strongly inhibited by serum due to nonnpecific IgG competing for binding of the therapeutics to FCγRIIIa on natural killer cells, which leads to the requirement of a significant amount of drug and very high costs associated with such therapies. Moreover, enhanced ADCC of non-fucosylated forms of therapeutic antibodies through improved FcγRIIIa binding is shown to be inhibited by the fucosylated counterparts. In fact, non-fucosylated therapeutic antibodies, not including the fucosylated forms, exhibit the strongest and most saturable in vitro and ex vivo ADCC among such antibody variants with improved FcγRIIIa binding as those bearing naturally occurring oligosaccharide heterogeneities and artificial amino acid mutations, even in the presence of plasma IgG. Robust stable production of completely non-fucosylated therapeutic antibodies in a fixed quality has been achieved by the generation of a unique host cell line, in which the endogenous α-1,6-fucosyltransferase (FUT8) gene is knocked out. Thus, the application of non-fucosylated antibodies is expected to be a

promising approach as next-generation therapeutic antibodies with improved efficacy, even when administrated at low doses in humans in vivo. Clinical trials using non-fucosylated antibody therapeutics are underway at present. .COPYRGT. 2006 Informa UK Ltd.

L12 ANSWER 14 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2007050033 EMBASE Monoclonal antibodies: A morphing landscape for therapeutics. Nicolaides N.C.; Sass P.M.; Grasso L.. N.C. Nicolaides, Morphotek Inc., 210 Welsh Pool Road, Exton, PA 19341, United States. nicolaides@morphotek.com. Drug Development Research Vol. 67, No. 10, pp. 781-789 2006.
Refs: 23.
ISSN: 0272-4391. E-ISSN: 1098-2299. CODEN: DDREDK
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20070301. Last Updated on STN: 20070301

AB The concept of using antibodies as therapeutics to cure human diseases was postulated nearly 100 years ago by Paul Ehrlich and subsequently enabled by the discovery of hybridoma technology by Kohler and Milstein in 1975. While the use of monoclonal antibodies (mAbs) as drugs that can specifically target a disease-associated antigen is compelling, it has taken a quarter century for these molecules to be adopted as bona fide therapeutic agents. Despite their slow pursuit in drug development during the pioneering years, it is now estimated that there are nearly 500 mAb-based therapies in development. Major factors that have influenced the acceptance of monoclonal antibodies as therapeutics include their drug safety profiles, technological advancements for facilitating mAb discovery and development, and market success. Early on, it was demonstrated that antibodies could elicit clinical benefit by antagonizing a specific antigen without the common side effects that are prevalent with small chemical entities due to their nonspecific effects on homeostatic biochemical pathways. In addition, the significant technological advances that the biotechnology industry has established for developing and producing monoclonal antibodies at commercial scale in a more efficient and cost-effective manner has broadly enabled their use as therapeutics. However, despite the beneficial pharmacologic advantages and technological advances, it has been the sheer market success that monoclonal antibody products have achieved over the past few years that has propelled their vast pursuit by the biopharmaceutical industry in light of their value-creating potential. Here we provide an overview of the monoclonal antibody industry and discuss evolving technologies and strategies that are being pursued to overcome challenges in the changing marketplace. .COPYRGT. 2007 Wiley-Liss, Inc.

L12 ANSWER 15 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2006291091 EMBASE [Biotherapies: Evolution or revolution?]. BIOTHERAPIES: EVOLUTION OU REVOLUTION?. Sibilia J.. J. Sibilia, Service de Rhumatologie, Hopital de Hautepierre, 1 avenue Moliere, 67098 Strasbourg Cedex, France. jean.sibilia@wanadoo.fr. Presse Medicale Vol. 35, No. 4 II, pp. 637-640 2006.
Refs: 22.
ISSN: 0755-4982. CODEN: PRMEEM
Pub. Country: France. Language: French.
Entered STN: 20060703. Last Updated on STN: 20061207
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L12 ANSWER 16 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2006310873 EMBASE Targeting signal transduction as a strategy to treat inflammatory diseases. O'Neill L.A.J.. L.A.J. O'Neill, School of Biochemistry and Immunology, Trinity College, Dublin 2, Ireland. laoneill@tcd.ie. Nature Reviews Drug Discovery Vol. 5, No. 7, pp. 549-563 2006.
Refs: 96.

ISSN: 1474-1776. E-ISSN: 1474-1784. CODEN: NRDDAG
N2070. Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 20060919. Last Updated on STN: 20060919

AB Inflammatory diseases are a major burden on humanity, despite recent successes with biopharmaceuticals. Lack of responsiveness and resistance to these drugs, delivery problems and cost of manufacture of biopharmaceuticals mean that the search for new anti-inflammatory agents continues. Progress in our understanding of inflammatory signalling pathways has identified new targets, notably in pathways involving NF-κB, p38 MAP kinase, T lymphocyte activation and JAK/STAT. Other targets such as transcription factor complexes and components of pathways activated by TNF, Toll-like receptors and Nod-like receptors also present possibilities, and might show efficacy without being limited by effects on host defence. The challenge is to place a value on one target relative to another, and to devise strategies to modulate them.

L12 ANSWER 17 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2006411779 EMBASE A review of antibody therapeutics and antibody-related technologies for oncology. Scallon B.J.; Snyder L.A.; Mark Anderson G.; Chen Q.; Yan L.; Weiner L.M.; Nakada M.T.. Dr. M.T. Nakada, Centocor, Mail Stop R-4-2, 200 Great Valley Parkway, Malvern, PA 19355, United States. Mnakada@cntus.jnj.com. Journal of Immunotherapy Vol. 29, No. 4, pp. 351-364 2006.
Refs: 130.
ISSN: 1524-9557. CODEN: JOIME7
00002371200607000000001. Pub. Country: United States. Language: English.
Entered STN: 20060908. Last Updated on STN: 20060908
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L12 ANSWER 18 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2006075249 EMBASE [Report from Great Britain]. BERICHT AUS GROssBRITANNIEN. Woodhouse R.J.. R.J. Woodhouse, 4 Swainswick Gardens, Bath, BA1 6TL, United Kingdom. roger.woodhouse77177@fsmail.net. Pharmazeutische Industrie Vol. 68, No. 1, pp. 89-93 2006.
ISSN: 0031-711X. CODEN: PHINAN
Pub. Country: Germany. Language: German.
Entered STN: 20060310. Last Updated on STN: 20060310
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L12 ANSWER 19 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2006149357 EMBASE A look back at the pharmaceuticals market 2005. Deregulation continues. Prescrire International Vol. 15, No. 82, pp. 75-79 2006.
ISSN: 1167-7422. CODEN: PRINFU
Pub. Country: France. Language: English. Summary Language: English.
Entered STN: 20060411. Last Updated on STN: 20060411

AB The Health authorities seem to be more concerned with the economic health of the pharmaceutical industry than with public health. Patients and caregivers counting on the authorities to return to their original mission: to protect public interests.

L12 ANSWER 20 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2006555347 EMBASE [Monoclonal antibodies: Ximab, zumab and umab as drugs]. MONOKLONALE ANTIKORPER: XIMAB, ZUMAB UND UMAB ALS ARZNEIMITTEL. Neye H.. Dr. H. Neye, KV Niedersachsen, Berliner Allee 22, 30175 Hannover, Germany. holger.neye@kvn.de. Pharmazeutische Zeitung Vol. 151, No. 43, pp. 18-28 26 Oct 2006.
ISSN: 0031-7136. CODEN: PZSED5
Pub. Country: Germany. Language: German.
Entered STN: 20061123. Last Updated on STN: 20061123

DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L12 ANSWER 21 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2006537937 EMBASE Monoclonals -The billion dollar molecules of the future. Wiles M.; Andreassen P.. Dr. M. Wiles, BioInvent International AB, Drug Discovery World Vol. 7, No. 4, pp. 17-23 2006.
ISSN: 1469-4344. Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 20061121. Last Updated on STN: 20061121

AB In 1975, two British scientists thought of creating a mouse antibody that could be replicated or 'cloned' to produce identical copies. Identical copies with identical modes of action had the potential to be a drug. They had launched what was to be one of biotechnology's best ideas. If the pair could mimic the immune system's 'seek and destroy' capability by pre-designing antibodies for all manner of disease targets, it should be possible to block or activate cellular activity to order. It was an elegant concept opening up a raft of therapeutic possibilities, particularly in the area of cancer. Here it might be possible to attach a chemotherapy drug to an antibody. The antibody's specificity for a particular disease target would guide the chemo drug only to the cancerous cells and not the healthy ones. The concept, therefore, was excellent, but the use of mice monoclonals had drawbacks. The human body did not like antibodies from mice anymore than it liked the flu virus, so the antibodies themselves triggered an immune response and were destroyed. This 'immunogenicity' issue was to occupy researchers for another 20 or so years before it became possible to craft a monoclonal antibody (mAb) that would be acceptable to the human immune system.

L12 ANSWER 22 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2006482122 EMBASE Engineered antibodies: A new tool for use in diabetes research. Padoa C.J.; Crowther N.J.. C.J. Padoa, Department of Chemical Pathology, University of the Witwatersrand, National Health Laboratory Service, Johannesburg, South Africa. carolyn.padoa@kcl.ac.uk. Diabetes Research and Clinical Practice Vol. 74, No. 2 SUPPL., pp. S51-S62 30 Nov 2006.
Refs: 96.
ISSN: 0168-8227. CODEN: DRCPE
S 0168-8227(06)00282-8. Pub. Country: Ireland. Language: English. Summary Language: English.
Entered STN: 20061027. Last Updated on STN: 20061027

AB A revolution has occurred in the field of antibody engineering since Kohler and Milstein described a technique for the production of monoclonal antibodies in 1975. Their paper paved the way for future discoveries which have culminated in the use of recombinant antibody fragments in the treatment of diseases and their widespread use in research. This article will highlight some of these advances (scFv and Fab production, phage and ribosome display) as well as looking at the different uses of these recombinant antibody fragments in research and the treatment/diagnosis of disease. In particular, we will focus on the role of rFabs in mapping disease specific epitopes in diabetic patients and the promise this holds for the future. The methodology of genetic engineering has made it possible to produce tailor-made antibodies which do not depend on animal vehicles. The applications of these rFab are widespread. Many developments in diabetes diagnostics have come through innovations in antibody technology. The further development of techniques for producing recombinant antibodies will ultimately lead to even greater improvements in therapeutics and diagnostics for a number of different human diseases. .COPYRGT. 2006 Elsevier Ireland Ltd. All rights reserved.

L12 ANSWER 23 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2006425776 EMBASE Therapy with immunoglobulin: applications for monoclonal antibodies. Stowell C.P.. C.P. Stowell, Massachusetts General Hospital, 55

Fruit Street, Boston, MA 02114-2696, United States. cstowell@partners.org. Journal of Infusion Nursing Vol. 29, No. 3 SUPPL., pp. S29-S44 2006. Refs: 125.
ISSN: 1533-1458. CODEN: JINOCS
00129804200605001000004. Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20060915. Last Updated on STN: 20060915

AB The ability of antibodies to recognize specific antigenic targets and trigger responses from the immune system has made them attractive candidates as therapeutic agents. Monoclonal and recombinant technology have made possible the development of a new class of therapeutic and diagnostic agents that combine the exquisite specificity of antibodies with biologic compatibility and protracted half-lives. This technology is just beginning to be explored and considerable evolution may be expected in the next few decades.

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2007077718 EMBASE IGF1R signalling and its inhibition. Riedemann J.; Macaulay V.M.. V.M. Macaulay, Cancer Research UK Laboratories, Weatherall Institute of Molecular Medicine, Oxford OX3 9DS, United Kingdom. macaulay@cancer.org.uk. Endocrine-Related Cancer Vol. 13, No. SUPPL. 1, pp. S33-S43 2006.
Refs: 102.
ISSN: 1351-0088. CODEN: ERCAE
Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 20070316. Last Updated on STN: 20070316

AB The type 1 IGF receptor (IGF1R) is a transmembrane tyrosine kinase that is frequently overexpressed by tumours, and mediates proliferation and apoptosis protection. IGF signalling also influences hypoxia signalling, protease secretion, tumour cell motility and adhesion, and thus can affect the propensity for invasion and metastasis. Therefore, the IGF1R is now an attractive anticancer treatment target. This review outlines the effects of IGF1R activation in tumour cells, and will describe the strategies that are available to block IGF signalling, both as investigational tools and as novel anti-cancer therapeutics. Design of specific IGF1R inhibitors has been problematic due to close homology with the insulin receptor, but recently it has proved possible to design selective IGF1R inhibitors. These compounds and IGF1R antibodies are showing promise in preclinical models of human cancer, and several agents are now in early phase clinical trials. Both classes of agents affect insulin receptor signalling, either by direct kinase inhibition or antibody-induced insulin receptor downregulation. This effect may lead to clinical toxicity, but could be therapeutically beneficial in blocking signalling via variant insulin receptors capable of a mitogenic response to IGF-II. Specificity for IGF1R targeting can be achieved by antisense and siRNA-mediated IGF1R downregulation; these approaches have undoubted utility as research tools, and may in future generate nucleic-acid-based therapeutics. It will be important to use data from preclinical and early clinical trials to establish the molecular correlates of sensitivity to IGF1R blockade, and the optimum means of combining this new approach with standard treatment modalities. .COPYRGT. 2006 Society for Endocrinology.

L12 ANSWER 25 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN

2005:1170719 Document No. 143:435304 Platelet biomarkers for the detection of disease. Folkman, Judah; Klement, Giannoula (CHILDREN'S Medical Center Corporation, USA). PCT Int. Appl. WO 2005103281 A2 20051103, 124 pp.
DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU,

MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-US14210 20050426. PRIORITY: US 2004-565286P 20040426; US 2004-598387P 20040802; US 2004-609692P 20040913; US 2004-633027P 20041203; US 2004-633613P 20041206.

AB The present inventors have surprisingly discovered that platelets sequester angiogenic regulators and prevent their degradation Thus, by analyzing levels of angiogenic regulators in platelets, it is now possible to detect angiogenic activity, even at an early stage. By monitoring for changes in angiogenic activity, the presence of cancer or other angiogenic diseases or disorders can be predicted.

L12 ANSWER 26 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN

2005:589025 Document No. 143:114039 Vaccines comprising human angiomotin and tumor antigen, angiogenic factor or antibody for treating cancer, inflammation and angiogenesis-related diseases. Kiessling, Rolf; Holmgren, Lars (Bioinvent International AB, Swed.). PCT Int. Appl. WO 2005061538 A2 20050707, 66 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-EP14573 20041220. PRIORITY: GB 2003-30079 20031220.

AB A vaccine for preventing formation of blood vessels, for example neoangiogenesis, as well as repressing existing vascularization associated with tumors and other diseases, comprising angiomotin, for example as a whole mol. or fragment thereof or encoded as a gene or mRNA, or administered as dendritic cells (DC cells) expressing angiomotin, which may be utilized to generate immune responses to the angiomotin mol. Inhibition of angiogenesis and delay in tumor outgrowth in animal models of cancer is achieved.

L12 ANSWER 27 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN

2005:588556 Document No. 143:115395 Preparation of derivatives of gambogic acid and analogs as activators of caspases and inducers of apoptosis. Cai, Sui Xiong; Jiang, Songchun; Zhang, Han-Zhong (Cytovia, Inc., USA). PCT Int. Appl. WO 2005060663 A2 20050707, 51 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US42292 20041217. PRIORITY: US 2003-530256P 20031218.

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention is directed to novel derivs. of gambogic acid (I) and analogs thereof. Thus, 2-(Dimethylamino)ethyl gambogate (II) was prepared from I via esterification with ClCH2CH2NMe2·HCl in the presence of KI and Cs2CO4. The present invention also relates to the discovery that novel derivs. of gambogic acid are activators of caspases and inducers of apoptosis. Therefore, the activators of caspases and inducers of apoptosis of this invention can be used to induce cell death in a variety of clin. conditions in which uncontrolled growth and spread of abnormal cells occurs. The bioactivity of II was determined [caspase

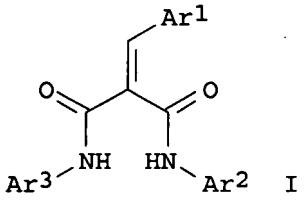
cascade activation EC50 = 676 nM vs. T-47D and EC50 = 1041 nM vs. DLD breast cancer cells; cell proliferation inhibition GI50 = 187 nM (vs. T-47D), GI50 = 173 nM (vs. DLD), GI50 = 101 nM (vs. MX-1), GI50 = 180 nM (vs. SW620), GI50 = 184 nM (vs. H1299), GI50 = 440 nM (vs. HEK293T), GI50 = 192 nM (vs. HEK293H)].

L12 ANSWER 28 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN
2005:493630 Document No. 143:42669 Immunogens comprising conformationally discriminating epitopes to produce FcγRIIb- or FcγRIIa-binding antibodies for diagnosis and therapy of neoplastic, infectious, immune and autoimmune diseases. Huber, Robert; Sondermann, Peter; Jacob, Uwe; Wendt, Kerstin; Chiara, Cabrele; Moroder, Luis (Max-Planck-Gesellschaft zur Foerderung der Wissenschaften E. V., Germany). PCT Int. Appl. WO 2005051999 A2 20050609, 57 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-EP13450 20041126. PRIORITY: EP 2003-27000 20031126.

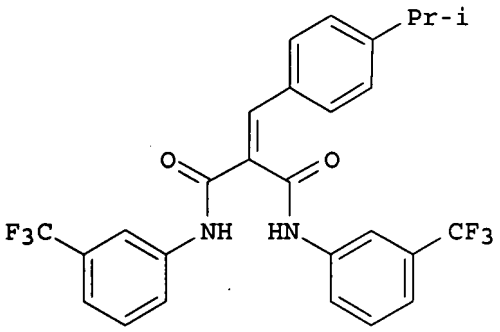
AB The invention relates to novel immunogens carrying conformationally discriminating epitopes (CDEs) and to immunization methods for producing antibodies that specifically recognize proteins with very closely related homologs. In particular, the invention relates to antibodies which are specific for either FcγRIIb or FcγRIIa.

L12 ANSWER 29 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN
2005:369221 Document No. 142:430024 Preparation of substituted 2-arylmethylene-N-aryl-N'-aryl-malonamides and analogs as activators of caspases and inducers of apoptosis. Cai, Sui Xiong; Pervin, Azra; Kasibhatla, Shailaja; Nguyen, Bao Ngoc (Cytovia, Inc., USA). PCT Int. Appl. WO 2005037196 A2 20050428, 140 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US32570 20041005. PRIORITY: US 2003-508290P 20031006.

GI



I



II

AB Substituted 2-arylmethylene-N-aryl-N'-aryl-malonamides and analogs I [wherein Ar1, Ar2, Ar3 = independently (un)substituted hetero/aryl, hetero/arylalkyl, (partially) saturated carbocyclic, heterocyclic] were prepared as activators of caspases and inducers of apoptosis for treating neoplasm. For example, II was prepared by acylation of with 3-aminobenzotrifluoride malonyl dichloride and reaction of the diamide with 4-isopropylbenzaldehyde. II exhibited caspase activation (EC50 = 15 nM for human breast cancer cell line T-47D), inhibition of cell proliferation (GI50 = 180 nM for T-47D). II induced apoptosis in Jurkat and T-47D cells. I can be used to induce cell death in a variety of clin. conditions in which uncontrolled growth and spread of abnormal cells occurs.

L12 ANSWER 30 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN

2005:216897 Document No. 142:298249 Use of siRNA for inhibiting GPC15 gene expression in treatment of cancer and other hyperproliferative disorders. O'Hagan, Ronan C.; Kannan, Karuppiah; Bailey, David (Genpath Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 2005021724 A2 20050310, 55 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US27968 20040827. PRIORITY: US 2003-498393P 20030827.

AB The present invention provides use of siRNA for inhibiting GPC15 gene expression in treatment of cancer and other hyperproliferative disorders and methods for diagnosis. Nonhuman mammals harboring a genetic modification relating to the GP115 gene, and their use as exptl. cancer models, are disclosed.

L12 ANSWER 31 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN

2005:177911 Document No. 142:259984 FcγRIIB-specific antibodies and fragments for enhancing efficacy of therapeutic antibodies or vaccines

against cancer, allergy, inflammation and autoimmune disease. Koenig, Scott; Veri, Maria-concetta (Macrogenics, Inc., USA). PCT Int. Appl. WO 2005018669 A1 20050303, 204 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US26071 20030818.

AB The present invention relates to antibodies or fragments thereof that specifically bind FcγRIIB, particularly human FcγRIIB, with greater affinity than said antibodies or fragments thereof bind FcγRIIA, particularly human FcγRIIA. The invention provides methods of enhancing the therapeutic effect of therapeutic antibodies by administering the anti-FcγRIIB antibodies or fragments to block the FcγRIIB-mediated inhibitory signaling of cell activation such as phagocytosis and respiratory burst. The invention also provides methods of enhancing efficacy of a vaccine composition by administering the antibodies of the invention.

L12 ANSWER 32 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN

2005:14184 Document No. 142:120497 Combination liposomal formulations comprising phospholipids. Jamil, Haris; Ahmad, Imran; Ahmad, Zafeer; Anyarambhatla, Gopal (Neopharm, Inc., USA). PCT Int. Appl. WO 2005000266 A2 20050106, 39 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US16413 20040522. PRIORITY: US 2003-472664P 20030522; US 2003-495260P 20030813.

AB The present invention provides a composition comprising a physiol. acceptable carrier and two or more agents encapsulated in a liposome, wherein the combination of the two or more agents possess the following properties: (1) cytotoxicity to tumor cells, (2) nutritional properties, (3) use in application to nails, hair, skin or lips, or (4) activity against parasites and insects. The invention also provides a method of making such a composition The invention further provides a method of treating cancer when the combination of the two or more agents is cytotoxic to tumor cells. For example, an initial formulation of liposome-encapsulated paclitaxel (LEP) was prepared containing phosphatidylcholine, cholesterol and cardiolipin. Sucrose and tocopherol were added to the formulation as stabilizers in order to form a sterilized lyophilized cake. Either doxorubicin (0.5 to 1.5 mg/mL) or mitoxantrone (0.5 to 1.5 mg/mL) was dissolved in water, and the solution was employed to reconstitute the lyophilized LEP cakes. The drug to lipid ratio varied from 1:120 to 1:24 (weight/weight) for doxorubicin and 1:120 to 1:24 (weight/weight) for mitoxantrone.

The reconstitution of the LEP cake with doxorubicin or mitoxantrone solution resulted in entrapment of either of the additive drugs (doxorubicin or mitoxantrone) into the liposomal formulation of paclitaxel (LEP). Moreover, 78 to 100% of the additive drug was entrapped into the LEP at a drug to lipid ratio of 1:120 to 1:15 for mitoxantrone and 1:120 to 1:24 for doxorubicin. Presence of an addnl. drug, doxorubicin or mitoxantrone, did not alter entrapment efficiency of paclitaxel in liposomes, size or stability of liposomes. Paclitaxel content remained intact after entrapping mitoxantrone or doxorubicin. This suggested that both drugs can coexist in a single delivery system without compromising size, entrapment efficiency or stability of the liposomal formulation.

L12 ANSWER 33 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN
2005:1005963 Document No. 143:279399 antiangiogenic compounds for treating disorders associated with vascular permeability. Soker, Shay; Satchi-Fainaro, Ronit (USA). U.S. Pat. Appl. Publ. US 2005203013 A1 20050915, 43 pp., Cont.-in-part of Appl. No. PCT/US03/11265. (English). CODEN: USXXCO. APPLICATION: US 2004-962723 20041012. PRIORITY: US 2002-371841P 20020411; WO 2003-US11265 20030411.

AB The invention relates to methods for decreasing or inhibiting disorders associated with vascular hyperpermeability and to methods of screening for compds. that affect permeability, angiogenesis and stabilize tight junctions. In one aspect of the invention there is provided a method of decreasing or inhibiting vascular hyperpermeability in an individual in need of such treatment. The method includes administering to the individual an effective amount of an antiangiogenic compound selected from the group consisting of endostatin, thrombospondin, angiostatin, tumstatin, arrestin, recombinant EPO and polymer conjugated TNP-470. Other antiangiogenic compds. are disclosed herein.

L12 ANSWER 34 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
2005458852 EMBASE Pharmacological manipulation of cell death: Clinical applications in sight?. Green D.R.; Kroemer G.. D.R. Green, Department of Immunology, St. Jude Children's Research Hospital, 332 North Lauderdale Street, Memphis, TN 38105, United States. douglas.green@stjude.org. Journal of Clinical Investigation Vol. 115, No. 10, pp. 2610-2617 2005.
Refs: 78.
ISSN: 0021-9738. CODEN: JCINAO
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20051103. Last Updated on STN: 20051103

AB This series of Reviews on cell death explores the creation of new therapies for correcting excessive or deficient cell death in human disease. Signal transduction pathways controlling cell death and the molecular core machinery responsible for cellular self-destruction have been elucidated with unprecedented, celerity during die last decade, leading to the design of novel strategies for blocking pathological cell loss or for killing unwanted cells. Thus, an increasing number of compounds targeting a diverse range of apoptosis-related molecules are being explored at the preclinical and clinical levels. Beyond the agents that are already FDA approved, a range of molecules targeting apoptosis-regulatory transcription factors, regulators of mitochondrial membrane permeabilization, and inhibitors or activators of cell death-related proteases are under close scrutiny for drug development.

L12 ANSWER 35 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
2005446075 EMBASE Selection, design, and engineering of therapeutic antibodies. Presta L.G.. Dr. L.G. Presta, Schering-Plough Biopharma, 901 California Avenue, Palo Alto, CA 94304, United States. leonard.presta@spcorp.com. Journal of Allergy and Clinical Immunology Vol. 116, No. 4, pp. 731-736 2005.
Refs: 52.
ISSN: 0091-6749. CODEN: JACIBY
S 0091-6749(05)01715-X. Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20051128. Last Updated on STN: 20051128

AB mAbs account for an increasing portion of marketed human biological therapeutics. As a consequence, the importance of optimal selection, design, and engineering of these not only has expanded in the past 2 decades but also is now coming into play as a competitive factor. This review delineates the 4 basic areas for optimal therapeutic antibody selection and provides examples of the increasing number of considerations necessary for, and options available for, antibody design. Though some of the advances in antibody technology (eg, antibodies derived from phage-display libraries) have already made it to market, other more recent advances, such as engineering antibodies for enhanced effector functions,

may not be far behind, especially given the increasing competition for therapeutic antibodies to the same target (eg, anti-CD20 and anti-TNF-α). .COPYRGT. 2005 American Academy of Allergy, Asthma and Immunology.

L12 ANSWER 36 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2006032654 EMBASE Development and regulation of monoclonal antibody products: Challenges and opportunities. Weinberg W.C.; Frazier-Jessen M.R.; Wen J.W.; Weir A.; Hartsough M.; Keegan P.; Fuchs C.. M.R. Frazier-Jessen, Division of Monoclonal Antibodies, Center for Drug Evaluation and Research, Food and Drug Administration, Bethesda, MD, Michelle.Jessen@fda.gov. Cancer and Metastasis Reviews Vol. 24, No. 4, pp. 569-584 2005.
Refs: 34.
ISSN: 0167-7659. CODEN: CMRED4
Pub. Country: Netherlands. Language: English. Summary Language: English.
Entered STN: 20060320. Last Updated on STN: 20060320

AB An increasing number of monoclonal antibodies for cancer diagnosis and treatment are in clinical use and in the development pipeline, with more expected as new molecular targets are identified. As with all drugs, product quality, an appropriate pre-clinical pharmacology-toxicology testing program, and well-designed clinical trials are essential for a successful drug development program. However, protein products such as monoclonal antibodies present unique regulatory concerns. The derivation from biological sources as well as the constantly evolving technologies utilized to develop these products demands continuous appraisal of safety concerns, even while the accumulated experience with these protein products has facilitated their safety evaluations. Because of the complex nature of these products and their inherent heterogeneity, a mechanistic understanding of the mode of action along with careful attention to product design and manufacture are critical to assuring a safe, effective and consistent product. Protein products may be highly species specific, thus pharmacologically relevant animal models are an important component in accurately assessing pre-clinical safety and establishing initial dosing. Furthermore, the immunogenicity of protein products can impact its safety profile, dose exposure, and efficacy. Mechanistic insight should form the basis of biological assays used for monitoring efficacy, safety, lot-to-lot consistency and manufacturing changes. The inherent uniqueness of each product necessitates a flexible case-by-case approach for biologies review that is based on a strong scientific understanding of relative risks. This review will provide an overview of approaches used in the development of antibody-based cancer therapeutics and the scientific basis of regulatory reviews. .COPYRGT. 2005 Springer Science + Business Media, Inc.

L12 ANSWER 37 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2005471527 EMBASE Biopharmaceuticals: Recent approvals and likely directions. Walsh G.. G. Walsh, Industrial Biochemistry Program, University of Limerick, Castletroy, Limerick City, Ireland. Gary.walsh@ul.ie. Trends in Biotechnology Vol. 23, No. 11, pp. 553-558 2005.
Refs: 36.
ISSN: 0167-7799. CODEN: TRBIDM
S 0167-7799(05)00194-0. Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 20051103. Last Updated on STN: 20051103

AB Some 160 biopharmaceuticals have now gained medical approval and several hundred are in the pipeline. Most are protein-based, although two nucleic acid-based products are now on the US/European market. An increasing proportion of approvals are engineered in some way and advances in alternative production systems and delivery methods will also likely impact upon the approvals profile over the remainder of this decade. .COPYRGT. 2005 Elsevier Ltd. All rights reserved.

L12 ANSWER 38 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2006032652 EMBASE Antibody-based therapeutics: Focus on prostate cancer. Ross J.S.; Gray K.E.; Webb I.J.; Gray G.S.; Rolfe M.; Schenkein D.P.; Nanus D.M.; Millowsky M.I.; Bander N.H.. J.S. Ross, Millennium Pharmaceuticals, Inc., Cambridge, MA, United States. rossj@mail.amc.edu. Cancer and Metastasis Reviews Vol. 24, No. 4, pp. 521-537 2005.
Refs: 98.
ISSN: 0167-7659. CODEN: CMRED4
Pub. Country: Netherlands. Language: English. Summary Language: English.
Entered STN: 20060320. Last Updated on STN: 20060320

AB The recent clinical and commercial success of anti-cancer antibodies such as rituximab, trastuzumab, cetuximab and bevacizumab has continued to foster great interest in antibody-based therapeutics for the treatment of both hematopoietic malignancies and solid tumors. Given the likely lower toxicity for antibodies which, in contrast with traditional cytotoxic small molecule drugs, target tumor cells and have a lower impact on non-malignant bystander organs, the potential increases in efficacy associated with conjugation to radioisotopes and other cellular toxins and the ability to characterize the target with clinical laboratory diagnostics to improve the drugs clinical performance, it is anticipated that current and future antibody therapeutics will find substantial roles alone and in combination therapy strategies for the treatment of patients with cancer. A significant number of cell surface proteins, glycoproteins, receptors, enzymes and peptides have been discovered that have become targets for the treatment of advanced hormone-refractory prostate cancer. A variety of naked antibodies and antibody conjugates have currently progressed through preclinical development and are in early or more advanced stages of clinical development. Clinicians, scientists and prostate cancer patients are all keenly interested to learn whether these agents when administered alone or in combination with other hormonal-based and cytotoxic therapies will show lasting benefit for sufferers of this common disease. .COPYRGT. 2005 Springer Science + Business Media, Inc.

L12 ANSWER 39 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2005083887 EMBASE Great company, bad stock. Jacobs T.. tom@completegrowth.com. Nature Biotechnology Vol. 23, No. 2, pp. 173 2005.
ISSN: 1087-0156. CODEN: NABIF
Pub. Country: United States. Language: English.
Entered STN: 20050310. Last Updated on STN: 20050310
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L12 ANSWER 40 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2005396799 EMBASE [Technologies of recombinant human antibodies]. LES TECHNOLOGIES DES ANTICORPS RECOMBINANTS HUMAINS. Mondon P.; Dubreuil O.; Bouayadi K.; Kharrat H.. P. Mondon, MilleGen, Prologue Biotech, rue Pierre et Marie Curie, 31682 Labege Cedex, France. philippe.mondon@millegen.com. Biofutur No. 258, pp. 34-40 2005.
Refs: 9.
ISSN: 0294-3506. CODEN: BIOFEM
Pub. Country: France. Language: French.
Entered STN: 20051006. Last Updated on STN: 20051006
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L12 ANSWER 41 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2006040069 EMBASE Monoclonal and recombinant antibodies, 30 years after.... Laffly E.; Sodoyer R.. R. Sodoyer, Research Department, Sanofi Pasteur, Campus Merieux, 69280 Marcy l'Etoile, France. regis.sodoyer@sanofipasteur.com. Human Antibodies Vol. 14, No. 1-2, pp. 33-55 2005.

Refs: 216.
ISSN: 1093-2607. CODEN: HUANFP
Pub. Country: Netherlands. Language: English. Summary Language: English.
Entered STN: 20060209. Last Updated on STN: 20060209

AB In 1975, the hybridoma technology provided, for the first time, an access to murine monoclonal antibodies. During the two following decades, their high potential, as laboratory tools, was rapidly exploited, but in vivo applications were still very limited. Nowadays, antibodies, omnipresent in both diagnostic and research domains, are largely invading the domain of therapy. A wide array of novel technologies, including phage display and transgenic mice, to isolate fully human antibodies and engineer these molecules, has been implemented. The natural propensity, of the antibody molecules, to metamorphosis makes them an ideal response to new applications and therapeutic challenges. The present review is a tentative update of the different antibody "formats" and a walk through the techniques recently applied to antibody engineering. In addition it also addresses some specific issues such as the development of expression systems suitable for large-scale production of recombinant antibodies.

L12 ANSWER 42 OF 88 EMBASE

2006144054 EMBASE Antibody engineering for the development of therapeutic antibodies. Kim S.J.; Park Y.; Hong H.J.. H.J. Hong, Laboratory of Antibody Engineering, Korea Research Institute of Bioscience and Biotechnology, Daejeon 305-333, Korea, Republic of. hjhong@kribb.re.kr. Molecules and Cells Vol. 20, No. 1, pp. 17-29 2005.
Refs: 100.
ISSN: 1016-8478. CODEN: MOCEEK
Pub. Country: Korea, Republic of. Language: English. Summary Language: English.
Entered STN: 20060424. Last Updated on STN: 20060424

AB Therapeutic antibodies represent one of the fastest growing areas of the pharmaceutical industry. There are currently 19 monoclonal antibodies in the market that have been approved by the FDA and over 150 in clinical developments. Driven by innovation and technological developments, therapeutic antibodies are the second largest biopharmaceutical product category after vaccines. Antibodies have been engineered by a variety of methods to suit a particular therapeutic use. This review describes the structural and functional characteristics of antibody and the antibody engineering for the generation and optimization of therapeutic antibodies.

L12 ANSWER 43 OF 88 EMBASE

2005139063 EMBASE Overview of biologic agents in medicine and dermatology. Sobell J.M.. Dr. J.M. Sobell, SkinCare Physicians of Chestnut Hill, 1244 Boylston Street, Chestnut Hill, MA 02467, United States. jsobell@skincarephysicians.net. Seminars in Cutaneous Medicine and Surgery Vol. 24, No. 1, pp. 2-9 2005.
Refs: 45.
ISSN: 1085-5629. CODEN: SCMSFR
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20050421. Last Updated on STN: 20050421

AB Three agents have recently been approved by the Food and Drug Administration for the treatment of chronic plaque **psoriasis**: alefacept, efalizumab, and etanercept. The field of dermatology has now entered a new era, joining other disciplines of medicine that have been using biologic agents for decades. These new therapies offer psoriatic patients the potential for safe and effective long-term management of this disease. This article reviews how an increased understanding of the pathophysiology of **psoriasis** led to the development of these products.

L12 ANSWER 44 OF 88 EMBASE

reserved on STN
2005399997 EMBASE Pharmacokinetics and concentration-effect relationships of therapeutic monoclonal antibodies and fusion proteins. Ternant D.; Paintaud G.. G. Paintaud, Francois-Rabelais University, UPRES EA 3853 'Immuno-Pharmaco-Genetics of Therapeutic Antibodies', Faculty of Medicine, 2 bis Boulevard Tonnelle, F 37032 Tours Cedex 1, France. paintaud@med.univ-tours.fr. Expert Opinion on Biological Therapy Vol. 5, No. SUPPL. 1, pp. S37-S47 2005.
Refs: 83.
ISSN: 1471-2598. CODEN: EOBTA2
Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 20051006. Last Updated on STN: 20051006
AB Although monoclonal antibodies (mAbs) constitute a major advance in therapeutics, their pharmacokinetic (PK) and pharmacodynamic (PD) properties are not fully understood. Saturable mechanisms are thought to occur in distribution and elimination of mAbs, which are protected from degradation by the Brambell's receptor (FcRn). The binding of mAbs to their target antigen explains part of their nonlinear PK and PD properties. The interindividual variability in mAb PK can be explained by several factors, including immune response against the biodrug and differences in the number of antigenic sites. The concentration-effect relationships of mAbs are complex and dependent on their mechanism of action. Interindividual differences in mAb PD can be explained by factors such as genetics and clinical status. PK and concentration-effect studies are necessary to design optimal dosing regimens. Because of their above-mentioned characteristics, the interindividual variability in their dose-response relationships must be studied by PK-PD modelling. .COPYRGT. 2005 Ashley Publications Ltd.

L12 ANSWER 45 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
2005399995 EMBASE Engineering of monoclonal antibodies and antibody-based fusion proteins: Successes and challenges. Teillaud J.-L.. J.-L. Teillaud, University Paris 6-Pierre and Marie Curie, Unite INSERM 255, Centre de Recherches Biomedicales des Cordeliers, 15 rue de l'Ecole de Medecine, 75270 Paris Cedex 06, France. jean-luc.teillaud@u255.bhdc.jussieu.fr. Expert Opinion on Biological Therapy Vol. 5, No. SUPPL. 1, pp. S15-S27 2005.
Refs: 100.
ISSN: 1471-2598. CODEN: EOBTA2
Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 20051006. Last Updated on STN: 20051006
AB Monoclonal antibodies (mAbs) and antibody-based fusion molecules have now come of age as therapeutics. Eighteen mAbs and two fusion molecules are on the market. mAbs directed against new targets are progressing at a rapid rate with the help of proteomics and genomics approaches. Many technical efforts have been made to generate a second-generation mAb with decreased immunogenicity and with optimised effector functions. The development of molecular engineering techniques applied to antibody molecules has also made it possible to design fusion molecules exhibiting different modules with bifunctional activities. Different approaches developed over the last two decades to generate and optimise therapeutic antibodies and antibody-based fusion molecules are described, with a particular focus on antibodies and fusion proteins used in oncology and inflammatory diseases. Some current technical challenges and trends are also discussed. .COPYRGT. 2005 Ashley Publications Ltd.

L12 ANSWER 46 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN
2004:965067 Document No. 141:406039 Combinations for the treatment of diseases involving cell proliferation, migration or apoptosis of myeloma cells, or angiogenesis. Hilberg, Frank; Solca, Flavio; Stefanic, Martin Friedrich; Baum, Anke; Munzert, Gerd; Van Meel, Jacobus C. A. (Boehringer Ingelheim International G.m.b.H., Germany; Boehringer Ingelheim Pharma

G.m.b.H. & Co. K.-G.). PCT Int. Appl. WO 2004096224 A2 20041111, 101 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-EP4363 20040424. PRIORITY: EP 2003-9587 20030429; EP 2004-508 20040113; EP 2004-1171 20040121.

AB The present invention relates to a pharmaceutical combination for the treatment of diseases which involves cell proliferation, migration or apoptosis of myeloma cells, or angiogenesis. The invention also relates to a method for the treatment of said diseases, comprising co-administration of effective amts. of specific active compds. and/or co-treatment with radiation therapy, in a ratio which provides an additive and synergistic effect, and to the combined use of these specific compds. and/or radiotherapy for the manufacture of corresponding pharmaceutical combination prepns. The pharmaceutical combination can include selected protein tyrosine kinase receptor antagonists and further chemotherapeutic or naturally occurring semisynthetic or synthetic agents.

L12 ANSWER 47 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN

2004:802862 Document No. 141:290028 Short interfering RNA (siRNA) containing locked nucleosides for treatment of cancer and SARS. Elmen, Joacim; Wahlestedt, Claes; Liang, Zicai; Sorensen, Anders Malling; Orum, Henrik; Koch, Troels (Santaris Pharma A/S, Den.). PCT Int. Appl. WO 2004083430 A2 20040930, 82 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-DK192 20040322. PRIORITY: DK 2003-442 20030321; US 2003-456888P 20030321; DK 2003-1625 20031031; DK 2004-145 20040130.

AB The present invention is directed to novel double-stranded short interfering (siRNA) analogs comprising locked nucleic acid (LNA) monomers. Such compds. induces sequence-specific post-transcriptional gene silencing in many organisms by a process known as RNA interference (RNAi). The compds. disclosed herein has improved properties compared to non-modified siRNAs and may, accordingly, be useful as therapeutic agents, e.g., in the treatment of cancers and severe acute respiratory syndrome (SARS). Thus, in vitro expts. showed that (1) 3'-end capping of siRNA antisense strands with ≥1 LNAs improves nuclease stability; (2) placing ≥1 LNAs at the 5'-end of the sense strand improves the potency of the siRNA; and (3) placing a thymidine or 5-methylcytidine LNA at positions 10 and/or 12 from the 5'-end in the sense strand reduces off-target effects. A highly preferred siRNA would therefore contain at least one LNA at the 5'-end and 3'-end of the sense strand and at least one LNA at the 3'-end of the antisense strand.

L12 ANSWER 48 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN

2004:681663 Document No. 141:201271 Antisense oligonucleotides for modulation of survivin gene expression and treatment of cancers. Hansen, Bo; Thrue, Charlotte Albaek; Petersen, Kamille Dumong; Westergaard, Majken; Wissenbach, Margit (Santaris Pharma A/S, Den.). PCT Int. Appl. WO 2004069991 A2 20040819, 122 pp. DESIGNATED STATES: W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR,

KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, ML, MR, NE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-DK96 20040210. PRIORITY: DK 2003-183 20030210; DK 2003-1708 20031118.

AB Oligonucleotides directed against the survivin gene are provided for modulating the expression of survivin. The compns. comprise oligonucleotides, particularly antisense oligonucleotides, targeted to nucleic acids encoding the survivin. Methods of using these compds. for modulation of survivin expression and for the treatment of diseases associated with either overexpression of survivin, expression of mutated survivin, or both, are provided. Examples of diseases are cancer such as lung, breast, colon, prostate, pancreas, lung, liver, thyroid, kidney, brain, testes, stomach, intestine, bowel, spinal cord, sinuses, bladder, urinary tract or ovaries cancers. The oligonucleotides may be composed of deoxyribonucleosides, or a nucleic acid analog (e.g., locked nucleic acid), or a combination thereof. Thus, 16-nucleotide antisense oligonucleotide gapmers containing phosphorothioate linkages throughout, β-D-oxy-LNA wings, and DNA cores were prepared These oligonucleotides, targeting various positions in the human TRX mRNA, inhibited TRX gene expression by 17 to 96% in prostate cancer cell lines.

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2004:606538 Document No. 141:156105 Mutated human antibodies having variant Fc region with altered affinity to FcγRIIIA and FcγRIIA for treating cancer, infection and autoimmune disease. Stavenhagen, Jeffrey; Vijh, Sujata (Macrogenics, Inc., USA). PCT Int. Appl. WO 2004063351 A2 20040729, 267 pp. DESIGNATED STATES: W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GH, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US643 20040109. PRIORITY: US 2003-439498P 20030109; US 2003-456041P 20030319; US 2003-514549P 20031023.

AB The present invention relates to mols., particularly polypeptides, more particularly Igs (e.g., antibodies), comprising a variant Fc region, wherein said variant Fc region comprises at least one amino acid modification relative to a wild-type Fc region, which variant Fc region binds FcγRIIIA and/or FcγRIIA with a greater affinity, relative to a comparable mol. comprising the wild-type Fc region. The mols. of the invention are particularly useful in preventing, treating, or ameliorating one or more symptoms associated with a disease, disorder, or infection. The mols. of the invention are particularly useful for the treatment or prevention of a disease or disorder where an enhanced efficacy of effector cell function (e.g., ADCC) mediated by FcγR is desired, e.g., cancer, infectious disease, and in enhancing the therapeutic efficacy of therapeutic antibodies the effect of which is mediated by ADCC.

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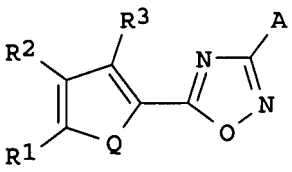
2004:565086 Document No. 141:123632 Preparation of 3,5-Disubstituted-[1,2,4]-oxadiazoles and analogs as activators of caspases and inducers of apoptosis. Cai, Sui Xiong; Zhang, Han-zhong; Kuemmerle, Jared D.; Zhang, Hong; Kemnitzer, William E. (Cytovia, Inc., USA). PCT Int. Appl. WO 2004058253 A1 20040715, 97 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English).

CODEN: PIXXD2. APPLICATION: WO 2003-US40308 20031218. PRIORITY: US 2002-433953P 20021218.

GI



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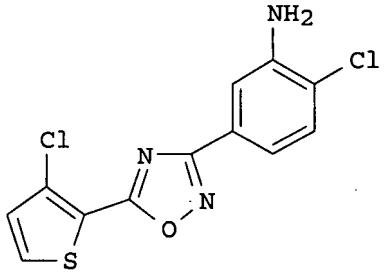

II

AB Title compds. I [R1-3 = H, halo, haloalkyl, aryl, etc.; Q = S, O, amino; A = heterocycle, carbocycle] are prepared For instance, 3-amino-4-chlorobenzamidoxime (preparation given) is reacted with 3-chlorothiophene-2-carbonyl chloride (pyridine, reflux, 50 min) to give II. II and other examples are potent caspase cascade activators and inducers of apoptosis in solid tumor cells, e.g., human breast cancer cell lines T-47D and ZR-75-1.

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2004:534300 Document No. 141:65094 Substituted 1-benzoyl-3-cyano-pyrrolo[1,2-a]quinolines and analogs as activators of caspases and inducers of apoptosis. Cai, Sui Xiong; Drewe, John A.; Jiang, Sungchun; Kasibhatla, Shailaja; Kuemmerle, Jared Daniel; Sirisoma, Nilantha Sudath; Zhang, Han-Zhong (Cytovia, Inc., USA). PCT Int. Appl. WO 2004055163 A2 20040701, 106 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US39550 20031212. PRIORITY: US 2002-432608P 20021212.

AB The invention discloses substituted 1-benzoyl-3-cyanopyrrolo[1,2-a]quinolines and analogs thereof. Compds. of the invention are activators of caspases and inducers of apoptosis. Therefore, the compds. of the invention can be used to induce cell death in a variety of clin. conditions in which uncontrolled growth and spread of abnormal cells occurs. Compound prepn is described.

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2004:493842 Document No. 141:48598 Human calcitonin receptor activity modifying protein genes GPC99 and GPC99a involved in hyperproliferative conditions, and methods and compns. for treating and diagnosing cancer. O'Hagan, Ronan C.; Kannan, Karuppiah; Wang, Rijian (Genpath Pharmaceuticals, Incorporated, USA). PCT Int. Appl. WO 2004050834 A2 20040617, 80 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US37813 20031126. PRIORITY: US 2002-429877P 20021127.

AB This invention provides methods and compns. for treating hyperproliferative conditions such as cancer using reagents relating to the GPC99 or GPC99a gene, which encodes calcitonin receptor activity modifying protein 2 or 3 (RAMP2 or RAMP3) resp. GPC99 and GPC99a are identified by MaSS (Mammalian Second Site Suppression) screening and are mapped to human chromosome 17q12-q21.1 and 7p13-p12 resp. The expression profile in a panel of human tumor cell lines shows that GPC99 and GPC99a gene is involved in hyperproliferative conditions such as cancer. Up-regulation of GPC99 and GPC99a contributes to tumorigenesis and tumor development in a mammal. RAMP2 and RAMP3, as type I transmembrane proteins, interact with, and serve as co-receptors for, calcitonin receptor-like receptor (CRLR) or adrenomedullin (ADM). An anti-RAMP2 antibody is raised in rabbit using 18-aa peptide spanning a nonconserved 7-amino acid peptide close to the transmembrane region in the extracellular domain of RAMP2, which is critical for CRLR binding and adrenomedullin signaling. This antibody can induce apoptosis of human cancer cell lines through Annexin V and Caspase 3 stimulation. Thus various oligonucleotides of GPC99 and GPC99a are claimed as targets of siRNAs for cancer therapy, and related models for cancer treatments are also described.

L12 ANSWER 53 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN
2004:430723 Document No. 141:1219 Gene GPC15 involved in hyperproliferative conditions, and methods and compositions for treating and diagnosing cancer. O'Hagan, Ronan C.; Kannan, Karuppiah (Genpath Pharmaceuticals, Incorporated, USA). PCT Int. Appl. WO 2004043408 A2 20040527, 78 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US36799 20031113. PRIORITY: US 2002-426489P 20021113.
AB This invention provides methods and compns. for treating hyperproliferative conditions such as cancer using reagents relating to the GPC15 gene (also known as GP15). GPC15 was identified by the Mammalian Second Site Suppression ("MaSS") screening system. GPC15 gene is involved in hyperproliferative conditions such as cancer. Up-regulation of GPC15 contributes to tumorigenesis and tumor maintenance in a mammal. The GPC15 gene encodes ribosomal protein L29 (RPL29), which is a component of the large 60S ribosomal subunit. It also functions as a cell surface heparin/heparin sulfate binding protein. The GPC15 gene is expressed ubiquitously. The expression, however, is decreased in certain head & neck cancer, pancreatic cancer and ovarian cancer.

L12 ANSWER 54 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN
2004:252340 Document No. 140:264487 Medicaments containing disorazoles and derivatives thereof for the treatment of benign and malignant tumors. Irschik, Herbert; Jansen, Rolf; Sasse, Florenz; Baasner, Silke; Schmidt, Peter; Gunther, Eckhard (Zentaris GmbH, Germany). PCT Int. Appl. WO 2004024149 A1 20040325, 30 pp. DESIGNATED STATES: W: AT, AU, BR, BY, CA, CN, CO, GE, HR, ID, IL, IN, IS, JP, KR, KZ, LT, LV, MK, MX, NO, NZ, PH, PL, RU, SG, UA, UZ, YU, ZA; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR. (German). CODEN: PIXXD2. APPLICATION: WO 2003-EP9329 20030822. PRIORITY: US 2002-405594P 20020824.
AB The invention discloses disorazole compds. which are used as medicaments, preferably in the treatment of tumors, especially in the case of drug resistance and in metastasizing carcinoma. Possible uses thereof are not restricted to tumor diseases.

L12 ANSWER 55 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN
2004:162782 Document No. 140:216175 FcγRIIB-specific antibodies and

fragments for diagnosis and treatment of cancer, inflammation, autoimmune disease, allergy and immune disease. Koenig, Scott; Veri, Maria-Concetta (Macrogenics, Inc., USA). PCT Int. Appl. WO 2004016750 A2 20040226, 174 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US25399 20030814. PRIORITY: US 2002-403266P 20020814.

AB The present invention relates to antibodies or fragments thereof that specifically bind FcγRIIB, particularly human FcγRIIB, with greater affinity than said antibodies or fragments thereof bind FcγRIIA, particularly human FcγRIIA. The antibodies are humanized or chimeric derivs. of mouse monoclonal antibody 3H7 and 2B6. The invention provides methods of enhancing the therapeutic effect of therapeutic antibodies by administering the antibodies of the invention to enhance the effector function of the therapeutic antibodies. The invention also provides methods of enhancing efficacy of a vaccine composition by administering the antibodies of the invention.

L12 ANSWER 56 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN

2004:41276 Document No. 140:105251 3,4-Dihydroisoquinolin-1-one derivatives as inducers of apoptosis. Gangloff, Anthony R.; Litvak, Joane; Pararajasingham, Keith; Sperandio, David (Axys Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 2004004727 A1 20040115, 107 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US21102 20030703. PRIORITY: US 2002-394094P 20020703.

AB The invention discloses 3,4-dihydroisoquinolin-1-one derivs. that are activators of caspases and inducers of apoptosis, as well as pharmaceutical compns. comprising these compds., and methods for treating cancer using these compds. Preparation of selected compds. of the invention is included.

L12 ANSWER 57 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN

2004:20448 Document No. 140:87676 Derivatives of gambogic acid and analogs as activators of caspases and inducers of apoptosis. Tseng, Ben; Sirisoma, Nilantha Sudath; Cai, Sui Xiong; Zhang, Han-Zhong; Kasibhatla, Shailaja; Ollis, Kristin P.; Drewe, John A. (Cytovia, Inc., USA). PCT Int. Appl. WO 2004002428 A2 20040108, 92 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US20668 20030701. PRIORITY: US 2002-392358P 20020701; US 2002-413649P 20020926.

AB The invention is directed to derivs. of gambogic acid and analogs thereof. Exemplary gambogic acid derivs. of the present invention include, among others, derivs. substituted in the C10 and C28 positions of gambogic acid. The present invention also relates to the discovery that certain preferred compds. of the invention are activators of caspases and inducers of

apoptosis. Therefore, the activators of caspases and inducers of apoptosis of this invention can be used to induce cell death in a variety of clin. conditions in which uncontrolled growth and spread of abnormal cells occurs.

L12 ANSWER 58 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2004136191 EMBASE IL-10-related cellular cytokines and their receptors: New targets for inflammation and cancer therapy. Dumont F.J.. F.J. Dumont, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, United States. Francis_dumont@merck.com. Expert Opinion on Therapeutic Patents Vol. 14, No. 3, pp. 281-299 2004.
Refs: 98.
ISSN: 1354-3776. CODEN: EOTPEG
Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 20040412. Last Updated on STN: 20040412

AB IL-10 is an important mediator of immunoregulation, which exerts potent immunosuppressive activity by downregulating monocytic cell and T cell activation. Recently, five novel human cytokines structurally related to IL-10 and designated IL-19, -20, -22, -24 and -26 have been identified through genomic methods. All are secreted α-helical proteins whose amino acid sequences show 20 - 30% identity to that of IL-10. Furthermore, all the known cell surface receptors utilised by these cytokines are heterodimers of transmembrane subunits that belong to the Class II cytokine receptor family and signal predominantly through Janus kinases (JAKs)-signal transducer and activator of transcription (STAT) pathways. Preliminary characterisation of the biological activities of these new IL-10 family members has demonstrated that they all lack the immunosuppressive activity of IL-10 but perform diverse roles in mediating inflammatory responses in a variety of tissues. In particular, IL-19, -20 and -22 may be involved in skin inflammation, such as **psoriasis.** Moreover, adenovirus expression of IL-24 has antitumour activity and is being evaluated for cancer gene therapy. The potential of these cytokines and their receptors as therapeutic targets for inflammatory or malignant diseases has prompted considerable interest in both academia and the biopharmaceutical industry. This article provides an updated overview of the molecular and functional properties of these molecules and discusses the associated patent literature. 2004 .COPYRGT. Ashley Publications Ltd.

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2004339524 EMBASE The role of functional genomics in selecting disease targets for antibody-based therapy. Davis C.G.. C.G. Davis, Abgenix Inc., 6701 Kaiser Drive, Fremont, CA 94566, United States. geoff.davis@abgenix.com. Drug Development Research Vol. 61, No. 3, pp. 155-171 2004.
Refs: 118.
ISSN: 0272-4391. CODEN: DDREDK
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20040902. Last Updated on STN: 20040902

AB Antibodies have clearly established themselves as comprising a significant segment of marketed drugs. The rapid evolution of technologies for generating antibodies and optimizing them for therapeutic applications has led to a succession of approvals over the last decade. The success of genomics in elucidating the contents of the human genome has provided a vast number of new potential targets for antibody therapy, Future development of antibody drugs will depend upon our ability to identify new targets from the tens of thousands of recently identified genes. This effort, too, will be technology-driven, This review provides a general overview of the technologies available for enabling new target selection, technologies that are collectively referred to as "functional genomics." For organizational purposes, the technologies are divided into the following broad categories: expression profiling, comparative genomics, loss of function strategies, proteomics, and computational biology,

Through judicious application of combinations of these functional genomics technologies, we can anticipate a steady stream of novel well-validated targets for antibody therapy for years to come. .COPYRGT. 2004 Wiley-Liss, Inc.

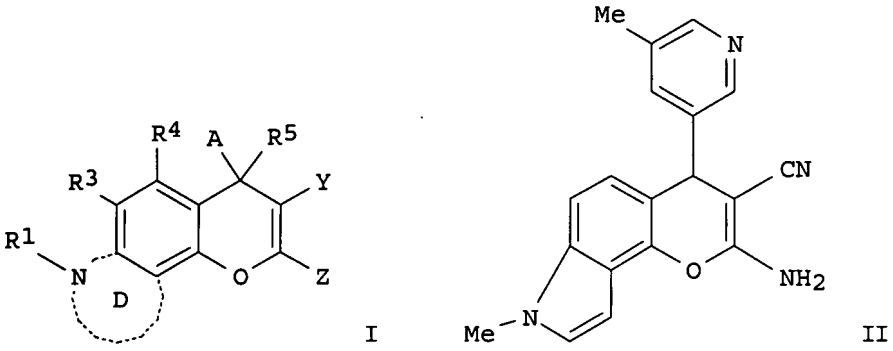
L12 ANSWER 60 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
2004339521 EMBASE The clinical pharmacology of therapeutic monoclonal antibodies. Roskos L.K.; Davis C.G.; Schwab G.M.. L.K. Roskos, Abgenix Inc., 6701 Kaiser Drive, Fremont, CA 94566, United States. lorin.roskos@abgenix.com. Drug Development Research Vol. 61, No. 3, pp. 108-120 2004.
Refs: 105.
ISSN: 0272-4391. CODEN: DDREDK
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20040902. Last Updated on STN: 20040902
AB Seventeen monoclonal antibodies are currently approved in the United States for therapeutic use in organ transplantation, percutaneous coronary intervention, prophylaxis of respiratory syncytial virus disease, rheumatoid arthritis, Crohn's disease, asthma, chronic lymphocytic leukemia, acute myeloid leukemia, non-Hodgkin's lymphoma, breast cancer, and colorectal cancer. All approved antibodies are of the IgG class. Thirteen are unconjugated intact antibodies, three are intact immunoconjugates, and one is a Fab fragment. Three of the antibodies are murine, five are chimeric, eight are humanized, and one is a fully human antibody generated by phage display technology. The antigen target and the structural and binding characteristics of the antibody determine the antibody's mechanism of action, pharmacokinetics, safety, and immunogenicity. Antibodies act through multiple mechanisms that include functional modulation of the antigen, recruitment of ADCC and CDC, and delivery of radionuclide or toxin payloads to target cells. Antibody half-life is usually governed by interaction with the FcRn receptor. In some cases, the antigen may act as a sink for antibody elimination. Safety profiles are determined by the pharmacology and tissue distribution of the target antigen, antibody isotype, the antibody payload, cytokine release, hypersensitivity reactions to xenogeneic protein, and immunogenicity. Fully human antibody technology may allow development of antibodies that have reduced risks of hypersensitivity reactions and immunogenicity, thereby enhancing safety and efficacy. The exquisite target specificity of antibodies, improvements in antibody engineering technology, and the wide availability of novel and validated therapeutic targets provide many current and future opportunities for the clinical development of therapeutic antibodies. .COPYRGT. 2004 Wiley-Liss, Inc.

L12 ANSWER 61 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
2005027526 EMBASE [News from drug research and development]. NEUES AUS ARZNEIMITTEL-FORSCHUNG UND -ENTWICKLUNG. Deutsche Apotheker Zeitung Vol. 144, No. 52, pp. 21-33 23 Dec 2004.
ISSN: 0011-9857. CODEN: DAZEA2
Pub. Country: Germany. Language: German.
Entered STN: 20050204. Last Updated on STN: 20050204
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L12 ANSWER 62 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN
2003:931479 Document No. 140:5049 Preparation of substituted 4-aryl-4H-pyrrolo[2,3-h]chromenes and analogs as activators of caspases and inducers of apoptosis and their uses against cancer and other disorders. Cai, Sui Xiong; Jiang, Songchun; Kemnitzer, William E.; Zhang, Hong; Attardo, Giorgio; Denis, Real (Cytovia, Inc., USA; Shire Biochem, Inc.). PCT Int. Appl. WO 2003097806 A2 20031127, 110 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU,

SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US15427 20030516. PRIORITY: US 2002-378079P 20020516.

GI



I II

AB The present invention is directed to substituted 4-aryl-4H-pyrrolo[2,3-h]chromenes and analogs thereof (shown as I; variables defined below; e.g. II). The present invention also relates to the discovery that compds. I are activators of caspases and inducers of apoptosis. Therefore, I can be used to induce cell death in a variety of clin. conditions in which uncontrolled growth and spread of abnormal cells occurs. The ability to activate the caspase cascade and induce apoptosis in human breast cancer cell lines T-47D and ZR-75-1 was measured for .apprx.50 examples of I, e.g. EC50 (nM) = 2.3 and 1.6, resp., for II. Although the methods of preparation are not claimed, .apprx.50 example prepns. are included. For I: R1 = alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, haloalkyl, alkoxyalkyl, aminoalkyl and oxiranylalkyl; R3 and R4 = H, halo, haloalkyl, aryl, fused aryl, carbocyclic, a heterocyclic group, a heteroaryl group, C1-10 alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, methylenedioxy, carbonylamido or alkylthio; R5 is H or C1-10 alkyl. A is (un)substituted and is aryl, heteroaryl, saturated carbocyclic, partially saturated carbocyclic, saturated heterocyclic, partially saturated heterocyclic or arylalkyl; D is (un)substituted and is a heteroarom., partially saturated (un)saturated heterocyclic fused ring, wherein said fused ring has 5 or 6 ring atoms, wherein one or two of said ring atoms are N atoms and the others of said ring atoms are C atoms. Y is CN, COR19, CO2R19 or CONR20R21, wherein R19, R20 and R21 = H, C1-10-alkyl, haloalkyl, aryl, fused aryl, carbocyclic, a heterocyclic group, a heteroaryl group, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl or aminoalkyl; or R20 and R21 are taken together with the N to form a heterocycle; and Z is NR22R23, NHCOR22N(COR23)2, N(COR22)(COR23), N:CHOR19 or N:CHR19 wherein R22 and R23 = H, C1-4 alkyl or aryl, or R22 and R23 are combined together with the group attached to them to form a heterocycle.

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2003:931119 Document No. 140:5041 Preparation of substituted 4H-chromenes, 2H-chromenes, chromans and analogs as activators of caspases and inducers of apoptosis and their uses against cancer and other disorders. Cai, Sui Xiong; Jiang, Songchun; Attardo, Giorgio; Denis, Real; Storer, Richard; Rej, Rabindra (Cytovia, Inc., USA; Shire Biochem, Inc.). PCT Int. Appl.

WO 2003096982 A2 20031127, 116 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US15432 20030516. PRIORITY: US 2002-378043P 20020516.

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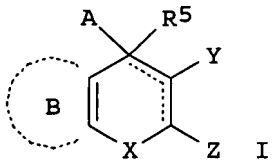

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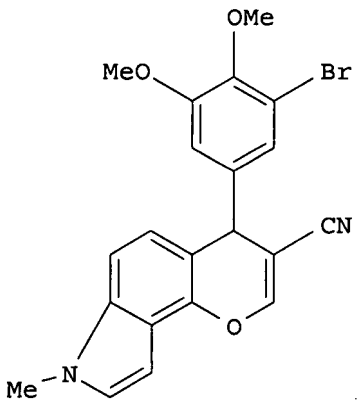

II

AB The present invention is directed to substituted 4H-chromenes, 2H-chromenes, chromans and analogs thereof (shown as I; variables defined below; e.g. II). The present invention also relates to the discovery that compds. I are activators of caspases and inducers of apoptosis. Therefore, I can be used to induce cell death in a variety of clin. conditions in which uncontrolled growth and spread of abnormal cells occurs. The ability to activate the caspase cascade and induce apoptosis in human breast cancer cell lines T-47D and ZR-75-1 was measured for .apprx.30 examples of I, e.g. EC50 (nM) = 2.7 and 2.2, resp., for II. Although the methods of preparation are not claimed, .apprx.30 example prepns. are included. For I: X is O, S or NR6, wherein R6 is H or (un)substituted alkyl; Y is H, halogen, CN, COR7, CO2R7 or CONRxRy, wherein R7, Rx and Ry = H, C1-10-alkyl, haloalkyl, aryl, fused aryl, carbocyclic, a heterocyclic group, a heteroaryl group, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl or aminoalkyl; or Rx and Ry are taken together with the N to which they are attached to form a heterocycle. Z is H, OH, OR8, OCOR8, wherein R8 is H, C1-10 alkyl, haloalkyl, aryl, fused aryl, carbocyclic, a heterocyclic group, a heteroaryl group, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl or aminoalkyl, when the dotted line between C atoms bonded to groups Y and Z is not present Z can be dialkyl. R5 is H or C1-10-alkyl; A is (un)substituted and is aryl, heteroaryl, saturated carbocyclic, partially saturated carbocyclic, saturated heterocyclic, partially saturated heterocyclic, arylalkyl or heteroarylalkyl; B is an (un)substituted aromatic or heteroarom. ring; and the dotted lines are single or double bonds, provided that both sets of dotted lines cannot be double bonds at the same time and R5 is not present when the dotted line between C atoms bonded to groups A and Y is a double bond.

L12 ANSWER 64 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN
2003:656581 Document No. 139:197370 Preparation of aryl ureas containing

pyridine, quinoline and isoquinoline N-oxide functionality as kinase inhibitors. Dumas, Jacques; Scott, William J.; Riedl, Bernd (Bayer Corporation, USA). PCT Int. Appl. WO 2003068229 A1 20030821, 67 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US4110 20030211. PRIORITY: US 2002-354935P 20020211.

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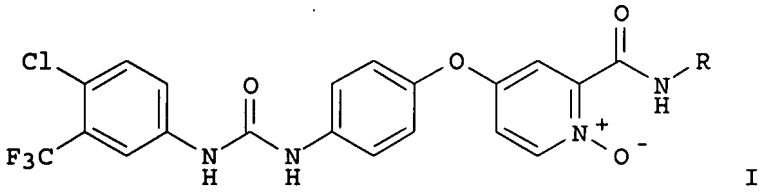

I

AB The title ureas containing a pyridine, quinoline, or isoquinoline functionality which is oxidized at the nitrogen heteroatom MLBNHCONHA [A = (un)substituted Ph, naphthyl, 5-6 membered monocyclic heteroaryl, 8-10 membered bicyclic heteroaryl; B = (un)substituted phenylene, naphthylene, 5-6 membered monocyclic heteroarylene, 8-10 membered bicyclic heteroarylene; L = (CH2)mO(CH2)l, (CH2)m(CH2)l, (CH2)mCO(CH2)l, etc.; m, l = 0-4; M = (un)substituted pyridine-1-oxide, quinoline-1-oxide, isoquinoline-1-oxide; with the provisos] which are useful in the treatment of (i) raf mediated diseases, for example, cancer, (ii) p38 mediated diseases such as inflammation and osteoporosis, and (iii) VEGF mediated diseases such as angiogenesis disorders, were claimed. Preparation of two ureas such as I [R = H, Me] which are not compds. of the invention, and have been distinguished from the compds. of the invention by a proviso, was described. Pharmaceutical composition comprising the title ureas was claimed.

L12 ANSWER 65 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN

2003:656575 Document No. 139:197476 Preparation of aryl heterocyclyl ureas with raf kinase and angiogenesis inhibiting activity. Dumas, Jacques; Scott, William J.; Elting, James; Hatoum-Makdad, Holia (Bayer Corporation, USA). PCT Int. Appl. WO 2003068223 A1 20030821, 142 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US4102 20030211. PRIORITY: US 2002-354948P 20020211.

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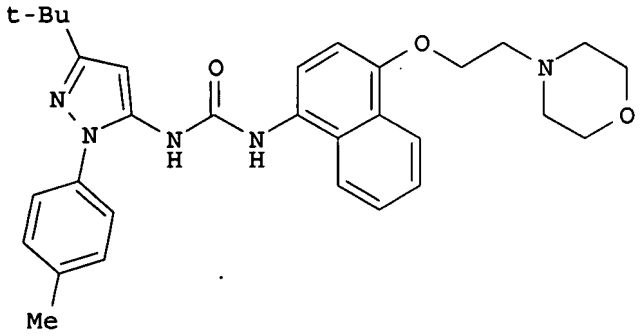

I

AB 283 Of the title ureas useful for treating diseases mediated by raf kinase and diseases mediated by the VEGF induced signal transduction pathway characterized by abnormal angiogenesis or hyperpermeability processes, were claimed. Synthesis of 6 ureas such as I was described. Thus, reacting 3-(tert-butyl)-1-(4-methylphenyl)pyrazole-5-ylamine with 4-(2-morpholin-4-ylethoxy)naphthylamine (prepns. given) and CDI in CH2Cl2 afforded 80% I which showed IC50 of < 1 μM in in vitro raf kinase and in in vitro Flk-1 ELISA assay.

L12 ANSWER 66 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN
2003:396849 Document No. 138:401758 Preparation of 5-substituted N-(1H-indazol-5-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amines as antiproliferative agents. Mastalerz, Harold; Zhang, Guifen; Tarrant, James G.; Vite, Gregory D. (Bristol-Myers Squibb Company, USA). PCT Int. Appl. WO 2003042172 A2 20030522, 74 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US36528 20021112. PRIORITY: US 2001-333014P 20011114.

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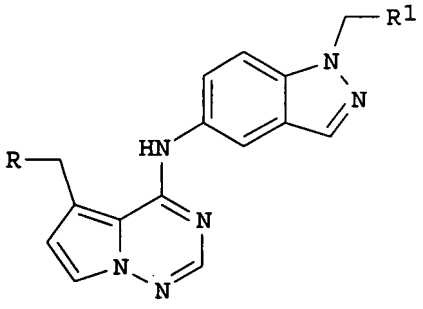

I

AB Title compds. I [wherein R = SR2, SOR2, SO2R2, OR2, or NR3R4; R1 = (un)substituted aryl or heterocyclyl; R2 = H or (un)substituted alkyl, aryl, aralkyl, or heterocyclyl; R3 and R4 = independently H or (un)substituted alkyl, aryl, or heterocyclyl; or NR3R4 = (un)substituted heterocyclyl; and enantiomers, diastereomers, and pharmaceutically acceptable salts, prodrugs, and solvates thereof] were prepared as

inhibitors of tyrosine kinase activity of growth factor receptors, such as HER1, HER2 and HER4. For example, coupling of 5-bromomethyl-4-chloropyrrolo[2,1-f][1,2,4]triazine with benzenethiol in the presence of diisopropylethylamine in DCM, followed by addition of 1-(3-fluorobenzyl)-1H-indazol-5-ylamine in BuOH and 1,2-dichloroethane gave the phenylthio derivative I (R = PhS; R1 = 3-FC6H4) (II) in 58% yield. Oxidation with 3-chloroperbenzoic acid in chloroform provided the sulfinyl derivative I (R = PhSO; R1 = 3-FC6H4) (III) in 95% yield. I inhibited HER-1, HER-2, and HER-4 kinases with IC50 values between 0.001 μM - 25 μM. Thus, I are useful as antiproliferative agents and for the treatment of other diseases associated with signal transduction pathways operating through growth factor receptors (no data).

L12 ANSWER 67 OF 88 EMBASE

2003425461 EMBASE Antibodies as therapeutic agents: Vive la renaissance!. Stockwin L.H.; Holmes S.. S. Holmes, Domantis Limited, Granta Park, Abington, Cambridge, CB1 6GS, United Kingdom. Expert Opinion on Biological Therapy Vol. 3, No. 7, pp. 1133-1152 2003.
Refs: 193.
ISSN: 1471-2598. CODEN: EOBTA2
Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 20031113. Last Updated on STN: 20031113

AB Until recently, the concept of antibodies as in vivo therapeutics was still considered to be an exceedingly ambitious goal. However, in 2003, the situation has been completely transformed, with 14 FDA-approved monclonal antibodies (mAbs), 70 in late stage clinical (Phase II+) trials and > 1000 in preclinical development. The driving force behind this reversal in fortune has been advances in antibody engineering and the emergence of novel discovery techniques which overcame stability and immunogenicity issues that had blighted previous clinical trials of murine antibodies. For indications as diverse as inflammation, cancer and infectious disease, it is clear that unique properties of antibodies make them safe, effective and versatile therapeutics. These drugs can be used to neutralise pathogens, toxins and endogenous mediators of pathology. As cell targeting reagents, antibodies can be used to modulate cytoplasmic cascades or to 'tag' specific cells for complement- or effector-mediated lysis. Antibodies can also be modified to deliver toxic or modulatory payloads (small molecules, radionuclides and enzymes) and engineered to bind multiple epitopes (bispecifics) or even to have novel catalytic activity (abzymes). The modular structure of immunoglobulins and the availability of antibody fragment libraries also make it possible to produce variable-domain therapeutics (Fab, single-chain and domain antibodies). Although exhibiting less favourable kinetics in vivo, these fragments are simple to express and have an increased tissue penetration, making them especially useful as neutralising agents or in the delivery of payload. The number of approved antibodies is expected to increase arithmetically in the near term, as the platform is adopted as a valid alternative to small molecule discovery. This review provides an introduction to the antibody discovery process and discusses the past, present and future applications of therapeutic antibodies, with reference to several FDA-approved precedents.

L12 ANSWER 68 OF 88 EMBASE

2004099464 EMBASE Emerging Roles of Targeted Small Molecule Protein-Tyrosine Kinase Inhibitors in Cancer Therapy. Smith J.K.; Mamoon N.M.; Duhe R.J.. R.J. Duhe, Dept. of Pharmacology and Toxicology, Univ. of Mississippi Medical Center, Jackson, MS 39216-4505, United States. RDUHE@pharmacology.umsmed.edu. Oncology Research Vol. 14, No. 4-5, pp. 175-225 2003.
Refs: 422.
ISSN: 0965-0407. CODEN: ONREE8
Pub. Country: United States. Language: English. Summary Language: English.

Entered STN: 20040318. Last Updated on STN: 20040318

AB Targeted protein-tyrosine kinase inhibitors (PTKIs) comprise a new, rapidly evolving class of low molecular weight anticancer drugs. Two members of this class, imatinib (Gleevec®) and gefitinib (Iressa®), are currently approved for market use in the United States. This review discusses the scientific history behind these two PTKI drugs, including the role of the targeted kinase in cancer etiology, the biochemistry of selective inhibition, the evaluation of clinical efficacy, and the mechanisms whereby drug resistance has emerged. Other PTKIs undergoing clinical evaluation are also described, including epidermal growth factor receptor kinase inhibitors (erlotinib, PKI166, and CI-1033) and PTKIs designed to disrupt tumor vascularization (SU5416, SU6668, SU11248, PTK787, and ZD6474). How might one apply current knowledge to the efficient development of new agents that would target as-yet-unexploited oncogenic PTKs such as chimeric anaplastic leukemia kinases or Janus kinases? Ideally, the targets should contain structurally distinct drug interaction epitopes, although it is not necessary that these epitopes be unique to a single target, because effective drugs may inhibit multiple kinases involved in an oncogenic process. Oral availability is a highly desirable feature because daily oral administration can maintain a sustained efficacious plasma concentration, whereas intermittent parenteral administration may not. Perhaps most importantly, one must verify the presence of an appropriate molecular target on a case-by-case basis before selecting a patient for PTKI therapy. Thus, the development of molecularly targeted diagnostic tools will be crucial to the ultimate success of molecularly targeted PTKI therapy.

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2003035732 EMBASE Engineered antibodies. Hudson P.J.; Souriau C.. P.J. Hudson, CSIRO Health Sciences and Nutrition, Parkville, Vic., Australia. peter.hudson@csiro.au. Nature Medicine Vol. 9, No. 1, pp. 129-134 1 Jan 2003.
Refs: 82.
ISSN: 1078-8956. CODEN: NAMEFI
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20030207. Last Updated on STN: 20030207

AB Engineered antibodies now represent over 30% of biopharmaceuticals in clinical trials, as highlighted by recent approvals from the US Food and Drug Administration. Recombinant antibodies have been reduced in size, rebuilt into multivalent molecules and fused with, for example radionuclides, toxins, enzymes, liposomes and viruses. The emergence of recombinant technologies has revolutionized the selection, humanization and production of antibodies, superseding hybridoma technology and allowing the design of antibody-based reagents of any specificity and for very diverse purposes.

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2003083939 EMBASE Oligos come of age. Lemaitre M.. Dr. M. Lemaitre, Eurogentec SA, Seraing, Belgium. m.lemaitre@eurogentec.com. Current Drug Discovery No. FEB., pp. 41-44 1 Feb 2003.
ISSN: 1472-7463. CODEN: CDDUAI
Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 20030306. Last Updated on STN: 20030306

AB Antisense oligonucleotides have come along way, and with a substantial number in late stage trials it is good to see the technology finally delivering on its promise. However, is the hype surrounding the new siRNA technologies justified? If their full advantages are to be realized, maybe scientists need to look back and learn from the past.

L12 ANSWER 71 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2003142284 EMBASE Pharma in the premier league. Croasdell G.. G. Croasdell, Thomson Current Drugs, 34-42 Cleveland Street, London W1T 4LB, United Kingdom. gary.croasdell@current-drugs.com. Current Drug Discovery No. MAR., pp. 35-39 1 Mar 2003.
ISSN: 1472-7463. CODEN: CDDUAI
Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 20030417. Last Updated on STN: 20030417
AB With some justification, the JP Morgan Hambrecht & Quist Annual Healthcare Conference can claim to be the premier event of its kind. After a turbulent 2002, what were the main themes to emerge from this year's meeting?

L12 ANSWER 72 OF 88 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
2004497593 EMBASE Translating angiogenesis research into the clinic: The challenges ahead. Augustin H.G.. Dr. H.G. Augustin, Dept. Vasc. Biol./Angiogenesis Res., Tumor Biology Center, Breisacher Str. 117, D-79106 Freiburg, Germany. augustin@angiogenese.de. British Journal of Radiology Vol. 76, No. SPEC. ISS. 1, pp. S3-S10 2003.
Refs: 57.
ISSN: 0007-1285. CODEN: BJRAAP
Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 20041209. Last Updated on STN: 20041209
AB The field of angiogenesis research has evolved to become one of the most rapidly growing biomedical disciplines. The interest in basic angiogenesis research is sparked by the translational therapeutic potential aimed at developing anti-angiogenesis as a novel therapeutic modality for tumours and a number of non-oncological diseases, such as rheumatoid arthritis, **psoriasis**, diabetic retinopathy and age-dependent macula degeneration. The molecular determinants of the angiogenic cascade have been characterized in great detail over the last few years. Likewise, intense ongoing efforts are aimed at identifying and validating additional vascular specific determinants that may be exploited as therapeutic targets for pro-angiogenic and anti-angiogenic therapy. At the same time, a large number of angiomodulatory compounds are in various phases of clinical trials. These include the neutralizing vascular endothelial growth factor (VEGF) antibody Avastin, which has successfully passed phase III clinical trials for the combination with chemotherapy in colorectal cancers. In view of the dramatic progress in basic angiogenesis research, surprisingly little is known about the nature of the neovasculature in human tumours. The inclusion and exclusion criteria of clinical trials of anti-angiogenic compounds are devoid of angiogenesis-related parameters and reliable biomarkers to trace the efficacy of an anti-angiogenic intervention are largely missing. Based on a brief review of the biology of the angiogenic cascade, this review provides an overview of the current concepts of the angiogenic vasculature in human tumours and discusses some key unanswered questions in translating angiogenesis research into the clinic. .COPYRGT. 2003 The British Institute of Radiology.

L12 ANSWER 73 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN
2002:946113 Document No. 138:24647 Preparation of 4-aryl-3-(3-aryl-1-oxo-2-propenyl)-2(1H)-quinolinones and analogs as activators of caspases and inducers of apoptosis for treatment of cancer and other proliferative disorders. Cai, Sui Xiong; Zhang, Han-Zhong; Drewe, John; Kasibhatla, Shailaja (Cytovia, Inc., USA). PCT Int. Appl. WO 2002098425 A1 20021212, 66 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT,

LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US17486 20020604. PRIORITY: US 2001-295007P 20010604.

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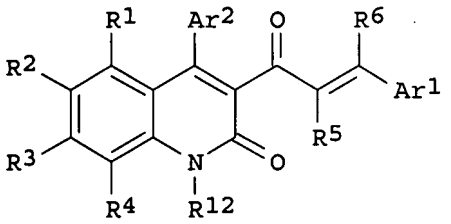

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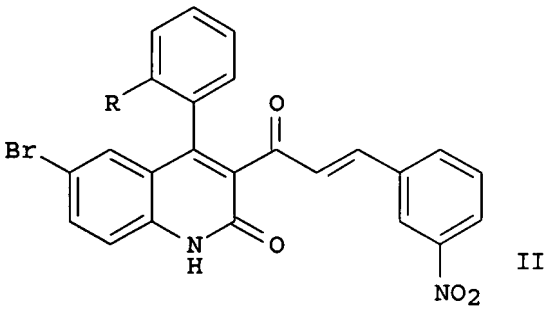

II

AB Title compds. I [wherein R1-R4 = independently H, halo, (hetero)aryl, (halo)alkyl, (hetero)cycloalkyl, alkenyl, alkynyl, (hetero)arylalkyl, (hetero)arylalkenyl, hydroxyalkyl, NO2, NH2, CN, acylamino, OH, SH, acyloxy, azido, (halo)alkoxy, aryloxy, arylalkoxy, carboxy, carbonylamido, or alkylthio; R5, R6, and R12 = independently H or (un)substituted alkyl; Ar1 = (un)substituted (hetero)aryl, (partially) saturated carbocyclyl, or (partially) saturated heterocyclyl; Ar2 = (un)substituted (hetero)aryl; and pharmaceutically acceptable salts or prodrugs thereof] were prepared as activators of caspases and inducers of apoptosis. For example, 2-amino-2'-fluoro-5-bromobenzophenone was treated with diketene in pyridine to give 3-acetyl-6-bromo-4-(2-fluorophenyl)-2(1H)-quinolinone (89%). Condensation with m-nitrobenzaldehyde in EtOH produced the (3-nitrophenylpropenoyl)quinolinone II (R = NO2) in 42% yield. A related compound, II (R = H), activated caspase cascade activity with EC50 values of 849 nM and 1800 nM against human breast cancer cell lines T-47D and ZR-75-1, resp. Thus, I may be used to induce cell death in a variety of clin. conditions in which uncontrolled growth and spread of abnormal cells occurs, such as cancer and other proliferative disorders.

L12 ANSWER 74 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN

2002:946109 Document No. 138:24718 Preparation of 4-substituted-1-(arylmethylidene)thiosemicarbazides and 4-substituted-1-(arylcarbonyl)thiosemicarbazides as activators of caspases and inducers of apoptosis. Cai, Sui Xiong; Nguyen, Bao Ngoc; Drewe, John; Reddy, P. Sanjeeva; Kasibhatla, Shailaja; Pervin, Azra (Cytovia, Inc., USA). PCT Int. Appl. WO 2002098420 A1 20021212, 93 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN,

TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US17108 20020531. PRIORITY: US 2001-294641P 20010601.

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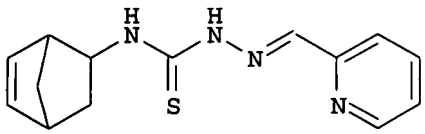

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AB The title compds. A1NR1C(:Q)NR2N:CR3A2 and A1NR1C(:Q)NR2NR3C(:O)A2 [A1, A2 = (un)substituted aryl, heteroaryl, etc.; Q = S, O; R1-R3 = H, alkyl, cycloalkyl] which may be used to induce cell death in a variety of clin. conditions in which uncontrolled growth and spread of abnormal cells occurs, were prepared Thus, reacting N1-bicyclo[2.2.1]hept-5-en-2-ylhydrazine-1-carbothioamide with 2-pyridinecarboxaldehyde in the presence of glacial AcOH in EtOH afforded 73% I which was identified as a potent caspase cascade activator and inducer of apoptosis in solid tumor cells (biol. data given).

L12 ANSWER 75 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN

2002:888735 Document No. 137:369971 Preparation of substituted 4H-chromenes and analogs as activators of caspases and inducers of apoptosis and their uses against cancer and other disorders. Cai, Sui Xiong; Zhang, Hong; Jiang, Songchun; Storer, Richard (Cytovia, Inc., USA). PCT Int. Appl. WO 2002092594 A1 20021121, 139 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US15399 20020516. PRIORITY: US 2001-290997P 20010516.

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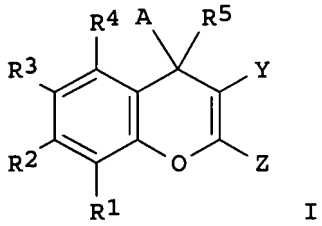

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AB The present invention is directed to substituted 4H-chromenes and analogs thereof (shown as I; e.g. 2-amino-3-cyano-7-hydroxy-4-(3-bromo-4,5-dimethoxyphenyl)-4H-chromene). It also relates to the discovery that I are activators of caspases and inducers of apoptosis and, therefore, can be used to induce cell death in a variety of clin. conditions in which controlled growth and spread of abnormal cells occurs. In I: R1-R4 = H, halo, haloalkyl, aryl, fused aryl, carbocyclic, heterocyclic, heteroaryl, C1-10 alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, methylenedioxy, carbonylamido or alkylthio; or R1 and R2, or R2 and R3, or R3 and R4, taken together with the atoms to which they are attached form

an aryl, heteroaryl, partially saturated carbocyclic or partially saturated heterocyclic group, wherein said group is optionally substituted. R5 is H or C1-10 alkyl; A is optionally substituted and is aryl, heteroaryl, saturated carbocyclic, partially saturated carbocyclic, saturated heterocyclic, partially saturated heterocyclic or arylalkyl; Y is CN, COR7, CO2R7 or CONRxRy, wherein R7, Rx and Ry = H, C1-10 alkyl, haloalkyl, aryl, fused aryl, carbocyclic, heterocyclic, heteroaryl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl or aminoalkyl; or Rx and Ry are taken together with the N to which they are attached to form a heterocycle; and Z is NR8R9, NHCOR8, N(COR9)2, N(COR8)(COR9), N:CHOR8 or N:CHR8, wherein R8 and R9 = H, C1-4 alkyl or aryl, or R8 and R9 are combined together with the group attached to them to form a heterocycle. The EC50 values for >80 I against T-47D and ZR-75-1 human breast cancer cell lines are tabulated, e.g. 30 and 25 nM, resp., for 2-amino-3-cyano-4-(3-bromo-4,5-dimethoxyphenyl)-4H-indolo[7,6-b]pyran. Although the methods of preparation are not claimed, 81 example prepns. are included.

L12 ANSWER 76 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN

2002:888548 Document No. 137:384750 Preparation of substituted coumarins and quinolinones as caspase activators for treatment of cancer. Cai, Sui Xiong; Zhang, Hong; Kemmitzer, William E.; Jiang, Songchun; Drewe, John A.; Storer, Richard (Cytovia, Inc., USA; Shire Biochem, Inc.). PCT Int. Appl. WO 2002092076 A1 20021121, 84 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US15401 20020516. PRIORITY: US 2001-290978P 20010516.

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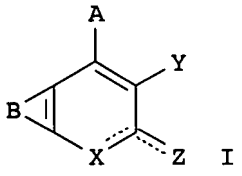

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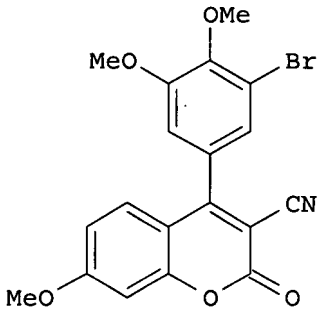

II

AB Title compds. I [wherein X = O, S or NR6; R6 = H or (un)substituted alkyl or aryl; Y = CN, COR7, CO2R7, or CONR9R10; R7, R9, and R10 = independently H, (halo)alkyl, (fused) aryl, carbocyclyl, heterocyclyl, heteroaryl, alkenyl, alkynyl, (hetero)arylalkyl, (hetero)arylalkenyl, (hetero)arylalkynyl, (hetero)cycloalkyl, hydroxyalkyl, or aminoalkyl; or NR9R10 = heterocyclyl; Z = O, S, halo, NR8, or NCOR8; R8 = independently H, alkyl, or aryl; A = (un)substituted (hetero)aryl, (hetero)cyclyl, or (hetero)arylalkyl; B = (un)substituted (hetero)aryl or (hetero)cyclyl; or pharmaceutically acceptable salts or prodrugs thereof] were prepared as caspase activators and inducers of apoptosis. For example, condensation of 5-bromoveratraldehyde with Et cyanoacetate in EtOH in the presence of piperidine gave 3-(3-bromo-4,5-dimethoxyphenyl)-2-cyanoacrylic acid Et ester. Treatment of the acrylate with a solution of 3-methoxyphenol and NaH in toluene afforded the coumarin II (1.7%). The latter induced apoptosis

in the human breast cancer cell lines T-47D and ZR-75-1 with EC50 values of 257 nM and 97 nM, resp. Therefore, I, optionally administered with at least one known cancer chemotherapeutic agent, are useful for the treatment of cancer.

L12 ANSWER 77 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN
2002:868695 Document No. 137:352786 Preparation of substituted N'-(arylcarbonyl)benzhydrazides and N'-(benzylidene)benzhydrazides and analogs as activators of caspases and inducers of apoptosis for use as antitumor agents. Cai, Sui Xiong; Kasibhatla, Shailaja; Drewe, John; Reddy, P. Sanjeeva; Zhang, Han-Zhong (Cytovia, Inc., USA). PCT Int. Appl. WO 2002089745 A2 20021114, 80 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US14722 20020510. PRIORITY: US 2001-289803P 20010510.

AB The present invention is directed to substituted N'-(arylcarbonyl)benzhydrazides, N'-(arylcarbonyl)benzylidene hydrazides and analogs thereof, represented by Ar1C(O)NR2NR1C(O)Ar2 and Ar1C(O)NR2N:CR1Ar2 (e.g. N'-(2-phenoxypyridine-3-carbonyl)-3-(trifluoromethyl)benzhydrazide (1)): wherein Ar1 is optionally substituted pyridyl, pyrimidinyl or phenyl; Ar2 is optionally substituted aryl or heteroaryl; and R1 and R2 are independently H, alkyl or cycloalkyl; with the proviso that said compound is other than 4-hydroxybenzoic acid (2-hydroxybenzylidene)hydrazide. The present invention also relates to the discovery that these compds. are activators of caspases and inducers of apoptosis and therefore may be used to induce cell death in a variety of clin. conditions in which uncontrolled growth and spread of abnormal cells occurs. Although the methods of preparation are not claimed, 42 example prepns. are included. Compound 1 and analogs were identified as caspase cascade activators and inducers of apoptosis in solid tumor cells and as antineoplastic compound that inhibits cell proliferation (GI50). Treatment with 1 leads to cell cycle arrest and apoptosis in T-47D cells. Compound 1 and analogs were identified as antineoplastic compound that selectively inhibits the proliferation of breast cancer cells (GI50). Compound 1 was also found to inhibit the clonogenic survival of T47D and MX-1 solid tumor cell lines.

L12 ANSWER 78 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN
2002:716246 Document No. 137:247550 Preparation of multifluoro-substituted chalcones and analogs as activators of caspases and inducers of apoptosis. Cai, Sui Xiong; Reddy, P. Sanjeeva; Drewe, John A.; Nguyen, Bao Ngoc; Kasibhatla, Shailaja (Cytovia, Inc., USA). PCT Int. Appl. WO 2002072544 A2 20020919, 53 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US7569 20020314. PRIORITY: US 2001-275473P 20010314.

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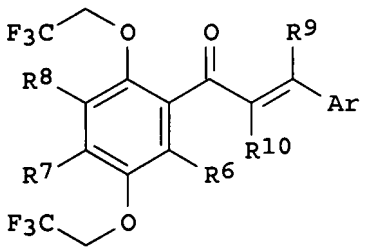

I

AB The title compds. [I; Ar = (un)substituted (hetero)aryl; R6-R10 = H, halo, haloalkyl, etc.] which are activators of caspases and inducers of apoptosis, and therefore may be used to induce cell death in a variety of clin. conditions in which uncontrolled growth and spread of abnormal cells occurs, were prepared Thus, reacting 2,5-bis(2,2,2-trifluoromethoxy)acetophenone with α,α,α-trifluoro-p-tolualdehyde afforded 13% I [Ar = 4-F3CC6H4; R6-R10 = H] which was identified as antineoplastic compound that inhibits cell proliferation in a variety of cancer cell lines (data given).

L12 ANSWER 79 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN

2002:465821 Document No. 137:47211 Substituted 2-aryl-4-arylaminopyrimidines and analogs as activators of caspases and inducers of apoptosis, their preparation, and the use thereof as, e.g., anticancer agents. Cai, Sui Xiong; Drewe, John A.; Nguyen, Bao; Reddy, P. Sanjeeva; Pervin, Azra (Cytovia, Inc., USA). PCT Int. Appl. WO 2002047690 A1 20020620, 210 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US47498 20011212. PRIORITY: US 2000-254581P 20001212.

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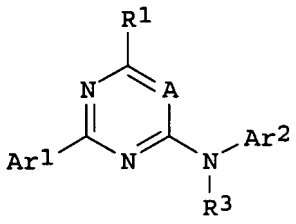

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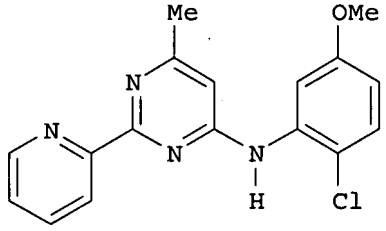


II

AB The invention is directed to substituted 2-aryl-4-(arylamino)pyrimidines I and analogs thereof [Ar1, Ar2 = (independently) optionally substituted aryl or heteroaryl; A = N or C-R2; R1, R2 = (independently) H, halo, haloalkyl, aryl, fused aryl, carbocyclic, heterocyclic, heteroaryl, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, nitro, amino, cyano, acylamido, OH, SH, acyloxy, N3, alkoxy, aryloxy, arylalkoxy, haloalkoxy, CO2H, carbonylamido, or alkylthio; and R3 = H, optionally substituted alkyl or cycloalkyl]. The invention also relates to the discovery that compds. I are activators of caspases and inducers of apoptosis. I may be used to induce cell death in a variety of clin. conditions in which uncontrolled growth and spread of abnormal cells

occurs. In particular, a method of treating disorders responsive to the induction of apoptosis, comprising administration of I, or a pharmaceutically acceptable salt or prodrug thereof, is claimed. Over 200 specific examples of I are described. For instance, condensation of 4-chloro-6-methyl-2-(2-pyridinyl)pyrimidine with 2-chloro-5-methoxyaniline gave title compound II in 44% yield. This compound induced apoptosis and activated caspase cascade in human breast cancer cell lines T-47D and ZR-75-1. Another compound I also showed marked selectivity for human breast cancer cells over other, non-breast cancer cell lines.

L12 ANSWER 80 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN
2002:449519 Document No. 137:28278 Methods of treatment of angiogenesis-related disease involving human MDA-7 protein. Chada, Sunil; Grimm, Elizabeth; Mhashilkar, Abner; Schrock, Bob; Rajagopal, Ramesh (University of Texas, USA). PCT Int. Appl. WO 2002045737 A2 20020613, 159 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US47215 20011207. PRIORITY: US 2000-254226P 20001207.

AB The invention relates to gene therapy methods for the treatment of human disease. More specifically, the invention is directed to methods for treating a subject with an angiogenesis-related disease. In one embodiment, an adenoviral expression construct comprising a nucleic acid encoding a human MDA-7 protein under the control of a promoter operable in eukaryotic cells, is administered to said patient with a angiogenesis-related disease. The present invention thus provides for treatment of angiogenesis-related disease by through expression of mda-7 and inhibition angiogenesis. Such diseases include cancer.

L12 ANSWER 81 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN
2002:353239 Document No. 136:374827 Receptor antagonist-lipid conjugates and delivery vehicles containing same. Ellens, Harma M.; Monck, Myrna A.; Yeh, Ping-Yang (Smithkline Beecham Corporation, USA). PCT Int. Appl. WO 2002036073 A2 20020510, 44 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US46206 20011029. PRIORITY: US 2000-245140P 20001102.

AB Vesicular drug delivery vehicles, such as liposomes, comprise a targeting ligand which comprises a non-biol., biomimetic antagonist to a receptor that is upregulated at a disease site, directly or indirectly chemical linked to a polar head group of a vesicle-forming lipid. The non-biol., biomimetic antagonist is an antagonist to a receptor upregulated in the vascular endothelium of inflammation, infection or tumor sites, selected from integrin receptors, prostate specific membrane antigen (PSMA) receptor, **herceptin**, Tie 1 and Tie 2 receptors, ICAM1, folate receptor, bFGF receptor, EGF receptor, VEGF receptor, PDGF receptor, etc. The vesicle-forming lipid is selected from phospholipids, sterols, glycolipids, cationic lipids, sphingolipids, glycerolipids, hydrophilic polymer derivs. of these lipids, gemini surfactants, etc. For example, liposomes were prepared containing lipid conjugates with a vitronectin receptor antagonist, (S)-7-[[N--(4-aminobutyl)-N-(benzimidazol-2-yl-methyl)]amino]carbonyl-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetic acid (preparation given) 0.5 mol%, DSPC 54.5 mol%, and

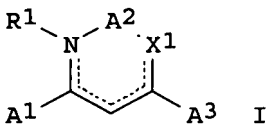
cholesterol 45 mol%. The liposomes were loaded with topotecan using ion gradient or polymer gradient loading/retaining techniques and administered to a patient diagnosed with ovarian cancer to inhibit growth of the cancerous tumor. A dosing regimen was 1.5 mg/m2 of the topotecan liposomes given as a 30 min infusion over the course of 1-3 days in a week for 2 wk in a 21 day cycle, repeated for 4 cycles.

L12 ANSWER 82 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN
2001:798040 Document No. 135:339222 Inhibition of abnormal cell proliferation with camptothecin or a derivative, analog, metabolite, or prodrug thereof, and combinations including camptothecin. Rubinfeld, Joseph (Supergen, Inc., USA). PCT Int. Appl. WO 2001080843 A2 20011101, 38 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US12848 20010419. PRIORITY: US 2000-553710 20000420.

AB A method for treating diseases associated with abnormal cell proliferation comprises delivering to a patient in need of treatment a compound selected from 20(S)-comptothecin, an analog of 20(S)-comptothecin, a derivative of 20(S)-camptothecin, a prodrug of 20(S)-camptothecin, and pharmaceutically active metabolite of 20(S)-camptothecin, in combination with an effective amount of one or more agents selected form the group consisting of alkylating agent, antibiotic agent, antimetabolic agent, hormonal agent, plant-derived agent, anti-angiogenesis agent and biol. agent. The method can be used to treat benign tumors, malignant or metastatic tumors, leukemia and diseases associated with abnormal angiogenesis.

L12 ANSWER 83 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN
2001:780869 Document No. 135:331449 Preparation of substituted 1,4-thiazepines and analogs as activators of caspases and inducers of apoptosis for treatment of cancer and other proliferative diseases. Cai, Sui Xiong; Drewe, John A.; Shelton, Emma Jane; Litvak, Joane; Sperandio, David; Spencer, Jeffrey R. (Cytovia, Inc., USA). PCT Int. Appl. WO 2001079187 A2 20011025, 162 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US12581 20010418. PRIORITY: US 2000-PV197599 20000418.

GI



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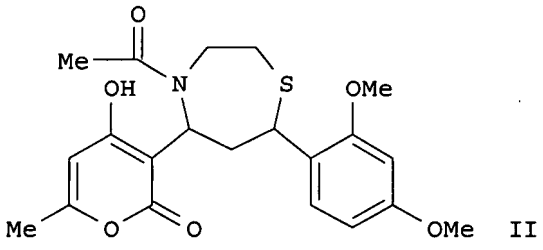


II

AB Title compds. I [wherein R1 = null, H, alkyl, or COR6; X1 = NR2, S, SO, SO2, or O; R6 = null, H, or (halo)alkyl; A1 = (un)substituted monocyclic

or fused polycyclic (hetero)aryl or (hetero)cycloalkyl ring; or A1 and R1 together form an (un)substituted fused polycyclic heteroaryl or heterocycloalkyl ring; the ring containing A2 = (un)substituted monocyclic or fused bicyclic heteroarylene or heterocycloalkylene ring; A3 = (un)substituted monocyclic or fused polycyclic (hetero)aryl or (hetero)cycloalkyl ring; and N-oxides, prodrugs, protected derivs., stereoisomers, and pharmaceutically acceptable salts thereof] were prepared as caspase activators and apoptosis inducers. For example, coupling of 3-acetyl-4-hydroxy-6-methylpyran-2-one with 2,4-dimethoxybenzaldehyde, followed by cyclization with 2-aminoethanethiol (61%) and acetylation, gave the [1,4]thiazepine II. Five invention compds. were tested and demonstrated caspase potency in human breast cancer cell lines T-47D and ZR-75-1 with EC50 values ranging from 345 nM to 6930 nM and 163 nM to 4207 nM, resp. Thus, I and their compns. with known cancer chemotherapeutic agents are useful for the treatment of drug resistant cancer in animals.

L12 ANSWER 84 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN

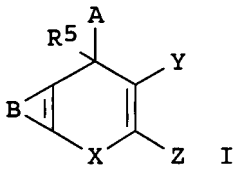
2001:380440 Document No. 135:18554 Targeted delivery of therapeutic and diagnostic moieties. Press, Michael; Park, Jinha (University of Southern California, USA). PCT Int. Appl. WO 2001036005 A2 20010525, 66 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US31424 20001115. PRIORITY: US 1999-PV165563 19991115.

AB Compns. and methods for improving cellular internalization of one or more compds. are disclosed. The invention provides a drug conjugate composition that can be delivered to a target cell, which comprises a carrier compound that has a binding specificity for a receptor mol. and is conjugated to a therapeutic or diagnostic moiety. When this composition is administered to a subject, the carrier compound binds to the receptor and is internalized by the target cell. Furthermore, monoclonal antibodies are disclosed that are internalized into target cells. The monoclonal antibodies of the invention are specific for target cells, particularly for cells expressing the surface antigen p185HER-2. The antibodies of the invention may be conjugated with a mol. for delivery into a target cell. Such mols. may be used for therapeutic treatment, including gene therapy, and for imaging. The invention also provides DNA sequences of the variable regions of particular monoclonal antibodies.

L12 ANSWER 85 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN

2001:359984 Document No. 134:353254 Substituted 4H-chromene and analogs as activators of caspases and inducers of apoptosis and the use thereof. Drewe, John A.; Cai, Sui Xiong; Wang, Yan (Cytovia, Inc., USA). PCT Int. Appl. WO 2001034591 A2 20010517, 148 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US30374 20001103. PRIORITY: US 1999-PV163584 19991105; US 2000-PV185211 20000224.

GI



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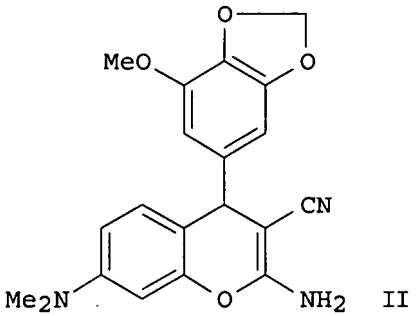

II

AB Title compds. (I) [wherein X = O or S; Y = CN, COR7, CO2R7, or CONRxRy; R7, Rx, and Ry = independently H, (halo)alkyl, (hetero)aryl, fused aryl, carbocyclic, heterocyclic, alkenyl, alkynyl, (hetero)arylalkyl, (hetero)arylalkenyl, (hetero)arylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, or aminoalkyl; or Rx and Ry taken together with the N to which they are attached form a heterocycle; Z = NR8R9, NHCOR8, N(COR8)2, N(COR8)(COR9), N:CHOR8, or N:CHR8; R8 and R9 = independently H, alkyl, or aryl; or R8 and R9 taken together with the group to which they are attached form a heterocycle; R5 = H or alkyl; A = (un)substituted (hetero)aryl, carbocyclic, heterocyclic, or arylalkyl; B = (un)substituted (hetero)aromatic ring] were prepared as activators of caspases and inducers of apoptosis. For example, piperidine was added to a mixture of 3-dimethylaminophenol, 5-methoxypiperonal, and malonitrile in EtOH to give II (74%). In assays against the human breast cancer cell lines T-47D and ZR-75-1, II showed potent caspase activity (determined as the ratios of net relative fluorescence units for test compds. compared to control samples of 5.5 and 6.3, resp.) and potency (EC50 = 87 nM and 38 nM, resp.). II also inhibited cell proliferation with GI50 values of 3 nM and 500 nM against T-47D and ZR-75-1, resp. Thus, I may be used to induce cell death in a variety of clin. conditions in which uncontrolled growth and spread of abnormal cells occurs.

L12 ANSWER 86 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN

2001:63858 Document No. 134:125935 Methods for treatment of hyperproliferative diseases using human MDA-7. Mhashilkar, Abner; Schrock, Bob; Chada, Sunil (Introgen Therapeutics, Inc., USA). PCT Int. Appl. WO 2001005437 A2 20010125, 161 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US19392 20000713. PRIORITY: US 1999-PV144354 19990715; US 2000-PV200768 20000428.

AB The present invention relates to gene therapy methods for the treatment of human disease. More specifically, the invention is directed, in one embodiment, to methods for treating a subject with a hyperproliferative disease. In another embodiment, an adenoviral expression construct comprising a nucleic acid encoding a human MDA-7 protein under the control of a promoter operable in eukaryotic cells is administered to the patient with a hyperproliferative disease. The present invention thus provides a gene therapy for treating hyperproliferative disease by elevating the expression of MDA-7 resulting in inhibition of cell growth and induction of apoptosis in hyperproliferative cells.

L12 ANSWER 87 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN

2001:851786 Document No. 136:4707 Immunostimulatory nucleic acids for inducing a Th2 immune response. McCluskie, Michael J.; Davis, Heather L.

(Can.). U.S. Pat. Appl. Publ. US 2001044416 A1 20011122, 50 pp. (English). CODEN: USXXCO. APPLICATION: US 2001-768012 20010122. PRIORITY: US 2000-177461P 20000120.

AB The invention relates to methods and products for inducing an immune response using immunostimulatory nucleic acids. In particular the immunostimulatory nucleic acids preferentially induce a Th2 immune response. The invention is useful for treating and preventing disorders associated with a Th1 immune response or for creating a Th2 environment for treating disorders that are sensitive to Th2 immune responses. These disorders include Th1-mediated disease, autoimmune disease, infection, and cancer.

L12 ANSWER 88 OF 88 CAPLUS COPYRIGHT 2007 ACS on STN

2000:534931 Document No. 133:150415 synthesis of gambogic acid analogs and derivatives as activators of caspases and inducers of apoptosis. Cai, Sui Xiong; Zhang, Han-Zhong; Wang, Yan; Tseng, Ben; Kasibhatla, Shailaja; Drewe, John A. (Cytovia, Inc., USA). PCT Int. Appl. WO 2000044216 A2 20000803, 123 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US2332 20000201. PRIORITY: US 1999-118102P 19990201; US 1999-135424P 19990521.

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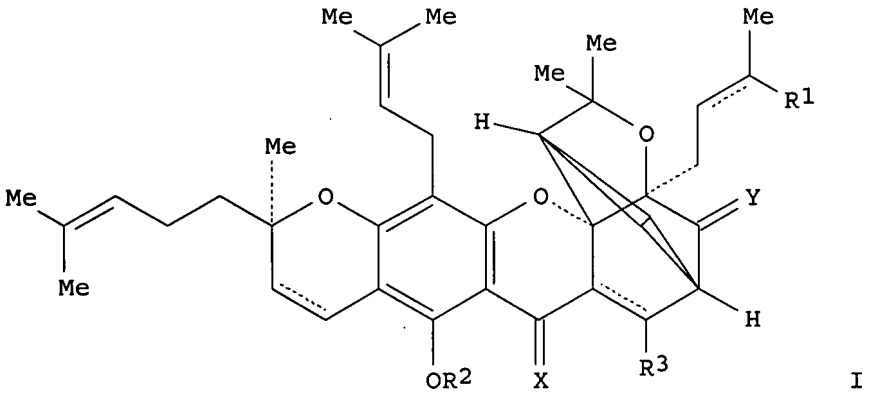

I

AB Synthesis of gambogic acid analogs and derivs. (I) [X, Y = =CH2, =O, (un)substituted =CHOH, alkoxymethinyl, =CHNH2, =NOH, (un)substituted =NNH2, =NCONH2; R1 = CHO, =CHOH, CO2H, acyl, (un)substituted alkoxycarbonyl, (un)substituted alkylthiocarbonyl, (un)substituted carbamyl, CONHOH, (un)substituted aryl, (un)substituted araaryl, (un)substituted heteroalkyl; R2 H, (un)substituted alkyl, acyl, carbamyl, sulfinyl; R3 = H, halogen, HO, (un)substituted alkyl, cycloalkyl, alkoxy, alkylthio, NH2] for use as activators of caspases and inducers of apoptosis is disclosed. Thus, gambogic acid is extracted from gamboge powder and reacted with the appropriate compds. to give I, e.g. piperidine to give I (R1 = piperidine; R2,R3 = H; dotted lines = double bonds) (II). II shows a GI50 of 50 nM in cell proliferation test and a LC50 of 50 nM in cell death assay against Y-47D. Therefore, I can be used to induce cell death in a variety of clin. conditions in which uncontrolled cell growth and spread of abnormal cells occurs.

=> s MAP kinase
L13 87290 MAP KINASE

=> s l13 and EGFR2
L14 1 L13 AND EGFR2

=> d l14 cbib abs

L14 ANSWER 1 OF 1 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN
2006:933657 The Genuine Article (R) Number: 086GB. Upregulation of fibroblast growth factor receptor 3 and epidermal growth factor receptors, in association with Raf-1, in urothelial dysplasia and carcinoma in situ after the Chernobyl accident. Romanenko A M; Morimura K; Kinoshita A; Wanibuchi H; Takahashi S; Zaparin W K; Vinnichenko W I; Vozianov A F; Fukushima S (Reprint). Ukraine Acad Med Sci, Dept Pathol, Inst Urol, Yu Kotzubinsky St 9A, UA-04053 Kiev, Ukraine (Reprint); Ukraine Acad Med Sci, Dept Pathol, Inst Urol, UA-04053 Kiev, Ukraine; Ukraine Acad Med Sci, Dept Urol, Inst Urol, UA-04053 Kiev, Ukraine; Osaka City Univ, Sch Med, Dept Pathol, Abeno Ku, Osaka 5458585, Japan; Nagoya City Univ, Grad Sch Med, Dept Expt Pathol & Tumor Biol, Mizuho Ku, Nagoya, Aichi 4678601, Japan. fukuchan@med.osaka-cu.ac.jp. CANCER SCIENCE (NOV 2006) Vol. 97, No. 11, pp. 1168-1174. ISSN: 1347-9032. Publisher: BLACKWELL PUBLISHING, 9600 GARSINGTON RD, OXFORD OX4 2DQ, OXON, ENGLAND. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The present study was carried out in order to examine the molecular status of selected growth factor receptors (GFR) in urinary bladder lesions, recently described by our group as representing 'Chernobyl cystitis'. Fibroblast growth factor receptor 3 (FGFR3), epidermal growth factor receptor 1 (EGFR1), EGFR2neu (a member of the same family), p53 and Raf-1 serine/threonine kinase expression were evaluated immunohistochemically in urinary bladder biopsies from 22 men with benign prostate hyperplasia (group 1). For comparison, 16 men with benign prostate hyperplasia and five women with chronic cystitis living in non-radio-contaminated areas of the country were also investigated as controls (group 2). Additionally, 14 patients with dysplasia, carcinoma in situ (CIS) and primary urothelial carcinoma (UC) operated before the Chernobyl accident as well as 23 patients with UC living in the radio-contaminated areas were included as pre- and post-Chernobyl UC groups 1 and 2, respectively. Chronic proliferative atypical cystitis ('Chernobyl cystitis') was observed in group 1 patients. Foci of dysplasia and CIS were found in 22 (100%) and 19 (86%) of the 22 cases, respectively; moreover, two small UC were also detected. Elevated levels of FGFR3, **EGFR2**/neu, p53 and to a lesser extent EGFR1 and Raf-1 expression in the urothelial dysplasia and CIS were evident for patients of group 1. Statistically significant differences in immunohistochemical scores for FGFR3, EGFR1, p53 and Raf-1 were observed between groups 1 and 2 and between group 1 and the post-Chernobyl UC group 2, where a change in expression of **EGFR2**/neu was also noted. A significant decrease in FGFR3 expression in additional pre-Chernobyl UC group 1 with dysplasia, CIS and UC compared with group 1 Chernobyl cystitis cases was detected. Our findings suggest that FGFR and EGFR signaling pathways, associated with p53 and Raf-1 activation, may contribute to multistage urothelial carcinogenesis caused by irradiation, through autocrine or paracrine growth stimulation.

=> s l13 and ErbB2
L15 376 L13 AND ERBB2

=> s l15 and antibod?
L16 72 L15 AND ANTIBOD?

=> s l16 and inhibit?
L17 51 L16 AND INHIBIT?

=> s l17 and psoriasis
L18 1 L17 AND PSORIASIS

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L18 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2007 ACS on STN
2004:467984 Document No. 141:22217 Therapy of non-malignant diseases or disorders with anti-**ErbB2 antibodies.** Sliwkowski, Mark X.; Brunetta, Paul G. (Genentech, Inc., USA). PCT Int. Appl. WO 2004048525 A2 20040610, 74 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US37367 20031121. PRIORITY: US 2002-428027P 20021121.

AB The authors disclose the preparation and biol. activity of murine and humanized **antibodies** to HER2. In one example, an anti-HER2 **antibody** is shown to **inhibit** heregulin-induced activation of Akt kinase and **erbB2** association with erbB3. The present application describes treatment of non-malignant indications, such as **psoriasis**, endometriosis, scleroderma, vascular diseases or disorders, respiratory disease, colon polyps or fibroadenoma, with anti-**ErbB2 antibodies** (e.g. rhuMAb 2C4).

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L19 36 DUP REMOVE L17 (15 DUPLICATES REMOVED)

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L19 ANSWER 1 OF 36 CAPLUS COPYRIGHT 2007 ACS on STN
2007:146214 Document No. 146:178399 Methods and kits for the prognosis of therapeutic success, recurrence free and overall survival in cancer therapies. Wirtz, Ralph Markus (Bayer Healthcare LLC, USA). PCT Int. Appl. WO 2007015947 A2 20070208, 129pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2006-US28230 20060720. PRIORITY: US 2005-703682P 20050729.

AB The invention provides novel compns., methods and uses, for the prediction, diagnosis, prognosis, prevention and treatment of malignant neoplasia and cancer. The present invention relates to methods for prognosis of therapeutic success of combinations of signal transduction **inhibitors**, therapeutic **antibodies**, radion- and chemotherapy in cancer therapy. The invention further relates to genes that are differentially expressed in tissue of cancer patients vs. those of normal "healthy" tissue. Differentially expressed genes for the identification of patients which are likely to respond to chemotherapy are also provided. The methods of the invention are based on determination of expression levels of 48 human genes which are differentially expressed prior to the onset of anti-cancer chemotherapy. The methods and compns. of the invention are most useful in the investigation of advanced colorectal cancer, but are useful in the investigation of other types of cancer and therapies as well.

L19 ANSWER 2 OF 36 CAPLUS COPYRIGHT 2007 ACS on STN
2006:120414 Document No. 144:184702 Gene expression profiles for identifying patients at risk of developing encephalitis following immunotherapy for Alzheimer's disease. O'Toole, Margot; Dorner, Andrew J.; Janszen, Derek B.; Slonim, Donna K.; Mounts, William M.; Reddy, Padmalatha S.; Hill, Andrew A. (Wyeth, USA). PCT Int. Appl. WO 2006014755 A2 20060209, 298 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-US25771 20050720. PRIORITY: US 2004-589877P 20040720; US 2005-672716P 20050418.

AB The present invention generally relates to a method for an improved treatment for Alzheimer's disease (AD) using immunotherapy, e.g., immunotherapy targeting β amyloid (Aβ) and immunotherapy based on AN1792. By ANOVA and GeneCluster analyses of Affymetrix U133A GeneChip data, statistically significant assocns. were detected between the gene expression profiles of peripheral blood mononuclear cells of patients prior to immunization with AN1792 and the post-immunization development of encephalitis. In addition, statistically significant assocns. were found between the pre-immunization gene expression profile in PBMCs and post-immunization development of IgG response. The method allows for predicting an adverse clin. response, and therefore allows for an improved safety profile of AN1792. In another embodiment, the method allows for predicting a favorable clin. response, and therefore allows for an improved efficacy profile of AN1792. The methods of the present invention may be combined to predict a favorable clin. response and the lack of an adverse clin. response.

L19 ANSWER 3 OF 36 CAPLUS COPYRIGHT 2007 ACS on STN
2006:837192 Document No. 145:448744 Novel targeted approaches to treating biliary tract cancer: the dual epidermal growth factor receptor and ErbB-2 tyrosine kinase **inhibitor** NVP-AEE788 is more efficient than the epidermal growth factor receptor **inhibitors** gefitinib and erlotinib. Wiedmann, Marcus; Feisthammel, Juergen; Bluethner, Thilo; Tannapfel, Andrea; Kamenz, Thomas; Kluge, Annett; Moessner, Joachim; Caca, Karel (Department of Internal Medicine II, University of Leipzig, Leipzig, Germany). Anti-Cancer Drugs, 17(7), 783-795 (English) 2006. CODEN: ANTDEV. ISSN: 0959-4973. Publisher: Lippincott Williams & Wilkins.

AB Aberrant activation of the epidermal growth factor receptor is frequently observed in neoplasia, notably in tumors of epithelial origin. Attempts to treat such tumors with epidermal growth factor receptor antagonists resulted in remarkable success in recent studies. Little is known, however, about the efficacy of this therapy in biliary tract cancer. Protein expression of epidermal growth factor receptor, ErbB-2, and vascular endothelial growth factor receptor-2 was assessed in seven human biliary tract cancer cell lines by immunoblotting. In addition, histol. sections from 19 patients with extrahepatic cholangiocarcinoma were analyzed for epidermal growth factor receptor, ErbB-2 and vascular endothelial growth factor receptor-2 expression by immunohistochem. Moreover, we sequenced the cDNA products representing the entire epidermal growth factor receptor coding region of the seven cell lines, and searched for genomic epidermal growth factor receptor amplifications and polysomy by fluorescence in-situ hybridization. Cell growth **inhibition** by gefitinib erlotinib and NVP-AEE788 was studied in vitro by automated cell counting. In addition, the anti-tumoral effect of erlotinib and NVP-AEE788 was studied in a chimeric mouse model. The anti-tumoral drug mechanism in this model was assessed by MIB-1 **antibody** staining, terminal deoxynucleotidyl transfer-mediated dUTP nick end-labeling assay, von Willebrand factor staining, and immunoblotting for p-p42/44 (p-Erk1/2,

p-MAPK) and p-AKT. Immunoblotting revealed expression of epidermal growth factor receptor, ErbB-2, and vascular endothelial growth factor receptor-2 in all biliary tract cancer cell lines. EGFR was detectable in six of 19 (32%) extrahepatic human cholangiocarcinoma tissue samples, ErbB-2 in 16 of 19 (84%), and vascular endothelial growth factor receptor-2 in nine of 19 (47%). Neither epidermal growth factor receptor mutations nor amplifications or polysomy were found in the seven biliary tract cancer cell lines. Gefitinib, erlotinib and NVP-AEE788 caused a significant growth **inhibition** in vitro; however, there was a significant difference in efficacy (NVP-AEE788>erlotinib>gefitinib). After 14 days of in-vivo treatment, using the chimeric mouse model, tumors had a significantly reduced volume and mass after NVP-AEE788, but not after erlotinib treatment, as compared with placebo. Reduction of proliferation (signaling via the mitogen-activated protein kinase pathway), induction of apoptosis and **inhibition** of angiogenesis were the main mechanisms of drug action. No significant reduction of anti-apoptotic AKT phosphorylation, however, occurred, which may be a possible counter mechanism of the tumor. Epidermal growth factor receptor, ErbB-2, and vascular endothelial growth factor receptor-2 expression was detectable in biliary tract cancer, and receptor **inhibition** exerts marked effects on tumor growth in vitro and in vivo, which was strongest for the dual EGFR/ErbB-2 **inhibitor** NVP-AEE788. Therefore, further clin. evaluation of this new drug for the treatment of biliary tract cancer is recommended.

L19 ANSWER 4 OF 36 CAPLUS COPYRIGHT 2007 ACS on STN

2005:121193 Document No. 142:214836 Biomarkers of cyclin-dependent kinase modulation in cancer therapy. Li, Martha; Rupnow, Brent A.; Webster, Kevin R.; Jackson, Donald G.; Wong, Tai W. (Bristol-Myers Squibb Company, USA). PCT Int. Appl. WO 2005012875 A2 20050210, 141 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US24424 20040729. PRIORITY: US 2003-490890P 20030729.

AB Biomarkers having expression patterns that correlate with a response of cells to treatment with one or more cdk modulating agents, and uses thereof. Transcription profiling was used to identify the biomarkers. Specifically, transcription profiling of the effect of a certain cdk2 **inhibitor** (BMS 387032 0.5 L-tartaric acid salt) on peripheral blood mononuclear cells was first performed. Gene chips were used to quantitate the levels of gene expression on a large-scale with Affymetrix human gene chips HG-U95A, B, and C. Next, profiling of a cdk2 **inhibitor**-treated tumor cell line A28780 at multiple doses and time points was performed to establish a correlation of tumor site response with peripheral blood biomarkers. In order to establish the mol. target-specificity of the potential biomarkers, tumor cell line A2780 treated with anti-cdk2 oligonucleotides was also profiles. Overlapping gene expression changes were selected for further evaluation in human ovarian carcinoma xenograft A2780 that were treated with the cdk2 **inhibitor.** The selected biomarkers were subjected to real-time PCR anal. in order to verify the observed changes from the gene chip anal. The biomarker comprising GenBank accession number W28729 was discovered to have the most consistent and robust regulation in response to cdk **inhibition.** Provided are methods for testing or predicting whether a mammal will respond therapeutically to a method of treating cancer that comprises administering an agent that modulates cdk activity.

L19 ANSWER 5 OF 36 CAPLUS COPYRIGHT 2007 ACS on STN

2005:71066 Document No. 142:170050 DEF domain-containing members of the **MAP kinase** pathway and their use in screening for drug

inhibitors. Blenis, John; Murphy, Leon O. (President and Fellows of Harvard College, USA). PCT Int. Appl. WO 2005007090 A2 20050127, 104 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US21514 20040702. PRIORITY: US 2003-484761P 20030703.

AB Mitogen-activated protein (**MAP**) **kinases** (e.g., ERK1/2) phosphorylate a variety of target proteins including, for example, several immediate-early gene products (e.g., Fos, Myc, and Jun family proteins). Certain phosphorylation reactions require binding of the **MAP kinase** to the DEF domain of the target protein. **Inhibitors** that block this interaction may be useful therapeutics for human disease, including as antineoplastic agents. This invention provides several advantages over known therapies that directly target the **MAP kinase** signaling cascade. Typically, most compds. that **inhibit** the **MAP kinase** pathway are non-specific and **inhibit** more than one enzyme, and the targeted **inhibited** kinases are not available to perform normal physiol. functions necessary for cell survival, whereas therapeutic methods of the present invention **inhibit** the activation of particular target proteins and leave the **MAP kinases** enzymically active and available to phosphorylate other non-DEF domain-containing proteins. Thus, DEF domains are identified in a large number of proteins, and the principles of the invention are exemplified using the immediate-early gene, c-Fos. Screening assays useful for identifying compds. that **inhibit** the **MAP kinase**-DEF domain interaction are also disclosed.

L19 ANSWER 6 OF 36 CAPLUS COPYRIGHT 2007 ACS on STN

2005:474827 Document No. 143:19968 Use of erralpha phosphorylation status as a breast cancer biomarker. Mertz, Janet E.; Ariazi, Eric A.; Kraus, Richard J. (USA). U.S. Pat. Appl. Publ. US 2005118658 A1 20050602, 18 pp. (English). CODEN: USXXCO. APPLICATION: US 2004-942387 20040916. PRIORITY: US 2003-504045P 20030919; US 2004-560350P 20040407.

AB The inventors discovered that the **ErbB2** signal transduction pathway can activate ERRα by inducing its phosphorylation. Based on this discovery, the present invention provides methods for determining whether a breast cancer patient is likely to respond to hormonal-blockade therapy or **ErbB2**-based therapy, methods for determining prognosis of breast cancer patients, methods for treating breast cancer, and methods for identifying agents that can modulate ERRα phosphorylation.

L19 ANSWER 7 OF 36 MEDLINE on STN

2005337186. PubMed ID: 15856022. Loss of RALT/MIG-6 expression in **ERBB2**-amplified breast carcinomas enhances ErbB-2 oncogenic potency and favors resistance to Herceptin. Anastasi Sergio; Sala Gianluca; Huiping Chen; Caprini Elisabetta; Russo Giandomenico; Iacovelli Stefano; Lucini Fabiana; Ingvarsson Sigurdur; Segatto Oreste. (Laboratory of Immunology, Regina Elena Cancer Institute, via Delle Messi d'Oro, 156/158, 00158, Rome, Italy.) Oncogene, (2005 Jun 30) Vol. 24, No. 28, pp. 4540-8. Journal code: 8711562. ISSN: 0950-9232. Pub. country: England: United Kingdom. Language: English.

AB An emerging paradigm holds that loss of negative signalling to receptor tyrosine kinases (RTKs) is permissive for their oncogenic activity. Herein, we have addressed tumor suppression by RALT/MIG-6, a transcriptionally controlled feedback **inhibitor** of ErbB RTKs, in breast cancer cells. Knockdown of RALT expression by RNAi enhanced the EGF-dependent proliferation of normal breast epithelial cells, indicating

that loss of RALT signalling in breast epithelium may represent an advantageous condition during ErbB-driven tumorigenesis. Although mutational inactivation of the RALT gene was not detected in human breast carcinomas, RALT mRNA and protein expression was strongly and selectively reduced in **ERBB2**-amplified breast cancer cell lines. Reconstitution of RALT expression in **ERBB2**-amplified SKBr-3 and BT474 cells **inhibited** ErbB-2-dependent mitogenic signalling and counteracted the ability of ErbB ligands to promote resistance to the ErbB-2-targeting drug Herceptin. Thus, loss of RALT expression cooperates with **ERBB2** gene amplification to drive full oncogenic signalling by the ErbB-2 receptor. Moreover, loss of RALT signalling may adversely affect tumor responses to ErbB-2-targeting agents.

L19 ANSWER 8 OF 36 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN

2005:551211 The Genuine Article (R) Number: 924ZA. **Inhibition** of HER-2 by three independent targeting strategies increases paclitaxel resistance of SKOV-3 ovarian carcinoma cells. Abuharbeid S; Apel J; Zugmaier G; Knabbe C; Sander M; Gilbert S; Czubayko F; Aigner A (Reprint). Univ Marburg, Sch Med, Dept Pharmacol & Toxicol, Karl von Frisch Str 1, D-35033 Marburg, Germany (Reprint); Univ Marburg, Sch Med, Dept Pharmacol & Toxicol, D-35033 Marburg, Germany; Univ Marburg, Sch Med, Dept Hematol Oncol, D-35033 Marburg, Germany; Robert Bosch Krankenhaus, Dept Lab Med, Stuttgart, Germany; Baxter Oncol GmbH, Frankfurt, Germany. aigner@staff.uni-marburg.de. NAUNYN-SCHMIEDEBERGS ARCHIVES OF PHARMACOLOGY (FEB 2005) Vol. 371, No. 2, pp. 141-151. ISSN: 0028-1298. Publisher: SPRINGER, 233 SPRING STREET, NEW YORK, NY 10013 USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Current treatment options for ovarian cancer, which is one of the most widespread gynecological malignancies, are limited, mainly because patients with advanced-stage disease often develop resistance to chemotherapeutics. In breast cancer cells, several studies suggest that overexpression of the human epidermal growth factor receptor-2 (HER-2) leads to increased resistance against certain, but not all cytotoxic drugs. In ovarian carcinoma, conflicting data on the correlation of HER-2 expression and tumor cell sensitivity exist. In this paper, we explore the role of HER-2 expression and signaling levels pertaining to paclitaxel (Taxol) chemoresistance by applying three different and independent strategies in SKOV-3 ovarian carcinoma cells. Firstly, we show that treatment with the HER-2 **inhibitory antibody** trastuzumab (Herceptin), which is well established in tumor therapy, results in markedly increased, rather than decreased, cellular paclitaxel resistance. Next, we present two newly developed low molecular weight **inhibitors** of HER-2 tyrosine kinase activity, D-69491 and D-70166. With both drugs, the decrease in cellular paclitaxel sensitivity upon HER-2 **inhibition** is confirmed. Finally, for more detailed analysis we stably downregulate HER-2 expression by ribozyme-targeting. Using clonal ribozyme-transfected SKOV-3 cells with different residual HER-2 levels, we establish a 'HER-2 gene dose effect' of paclitaxel cytotoxicity. We show that this effect is due to differential induction of apoptosis and differential cell cycle **inhibition** by paclitaxel. Finally, paclitaxel- or HER-2-mediated alterations in the phosphorylation of **MAP kinases** p42/44, Stress-activated protein kinase/Jun-terminal kinase (SAPK/JNK), and p38, and effects on the activation of caspase-3, caspase-7, and bcl-2 are discussed. We conclude that paclitaxel cytotoxicity in SKOV-3 cells is 'HER-2 dose-dependent' and identify cell proliferation as one underlying cellular event of this effect.

L19 ANSWER 9 OF 36 CAPLUS COPYRIGHT 2007 ACS on STN

2004:838610 Document No. 141:312238 DNA microarray analysis of gene expression in the diagnosis of estrogen receptor positive- and negative-breast cancer. Erlander, Mark G.; Ma, Xiao-Jun; Wang, Wei; Wittliff, James L. (Arcturus Bioscience, Inc., USA). PCT Int. Appl. WO 2004079014 A2 20040916, 226 pp. DESIGNATED STATES: W: AE, AG, AL, AM,

AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, CN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, ML, MR, NE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-XA6736 20040304. PRIORITY: US 2003-451942P 20030304; WO 2004-US6736 20040304.

AB The invention relates to the identification and use of gene expression profiles, or patterns, suitable for identification of populations that are pos. and neg. for estrogen receptor expression. The gene expression profiles may be embodied in nucleic acid expression, protein expression, or other expression formats, and may be used in the study and/or diagnosis of cells and tissue in breast cancer as well as for the study and/or determination of prognosis of a patient, including breast cancer survival.

L19 ANSWER 10 OF 36 CAPLUS COPYRIGHT 2007 ACS on STN

2004:467984 Document No. 141:22217 Therapy of non-malignant diseases or disorders with anti-**ErbB2 antibodies.** Sliwkowski, Mark X.; Brunetta, Paul G. (Genentech, Inc., USA). PCT Int. Appl. WO 2004048525 A2 20040610, 74 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US37367 20031121. PRIORITY: US 2002-428027P 20021121.

AB The authors disclose the preparation and biol. activity of murine and humanized **antibodies** to HER2. In one example, an anti-HER2 **antibody** is shown to **inhibit** heregulin-induced activation of Akt kinase and **erbB2** association with erbB3. The present application describes treatment of non-malignant indications, such as psoriasis, endometriosis, scleroderma, vascular diseases or disorders, respiratory disease, colon polyps or fibroadenoma, with anti-**ErbB2 antibodies** (e.g. rhuMAb 2C4).

L19 ANSWER 11 OF 36 CAPLUS COPYRIGHT 2007 ACS on STN

2004:41229 Document No. 140:105266 Boroproline compound combination therapy for various diseases. Adams, Sharlene; Miller, Glenn T.; Jesson, Michael I.; Jones, Barry (Point Therapeutics, Inc., USA). PCT Int. Appl. WO 2004004661 A2 20040115, 125 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US21547 20030709. PRIORITY: US 2002-394856P 20020709; US 2002-414978P 20021001; US 2003-466435P 20030428.

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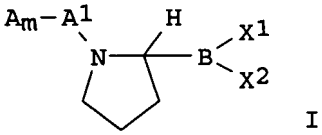

I

AB A method is provided for treating subjects with combination therapy including compds. of Formula I (wherein m is an integer between 0 and 10, inclusive; A and A1 may be L- or D-amino acid residues, the C bonded to B is in the L-configuration, and each X1 and X2 is, independently, a hydroxy group or a group capable of being hydrolyzed to a hydroxy group in aqueous solution at physiol. pH). It was surprisingly discovered that this combination enhanced the efficacy of both agents, and that administration of Formula I compds. induced cytokine and chemokine production in vivo. The combinations can be used to enhanced ADCC, stimulate immune responses and /or patient and treat certain disorders. The invention also relates to kits and compns. relating to such combinations.

L19 ANSWER 12 OF 36 CAPLUS COPYRIGHT 2007 ACS on STN

2004:964911 Document No. 141:389920 Systems and methods for characterizing a biological condition or agent using calibrated gene expression profiles. Bevilacqua, Michael P.; Cheronis, John C.; Tryon, Victor; Bankaitis-Davis, Danute M. (USA). U.S. Pat. Appl. Publ. US 2004225449 A1 20041111, 90 pp., Cont.-in-part of U.S. Ser. No. 821,850. (English). CODEN: USXXCO. APPLICATION: US 2004-781558 20040217. PRIORITY: US 1999-141542P 19990628; US 2000-195522P 20000407; US 2000-605581 20000628; US 2001-821850 20010329.

AB Methods are provided for evaluating a biol. condition of a subject using a calibrated profile data set derived from a data set having a plurality of members, each member being a quant. measure of the amount of a subject's RNA or protein as distinct constituents in a panel of constituents. The biol. condition may be a naturally occurring physiol. state or may be responsive to treatment of the subject with one or more agents. Calibrated profile data sets may be used as a descriptive record for an agent. The index was determined with resp. to a relevant population which has in common property that is at least one of age group, gender, ethnicity, geog. location, diet,medical disorder, clin. indicator, medication, phys. activity, body mass, and environmental exposure. The biol. conditions include inflammation, diabetes, prostate health or disease, manifested skin, liver metabolism and disease, vascular disease, abnormal cell development, cancer and infectious disease. The method can be used for evaluating the effect on a biol. condition by drugs.

L19 ANSWER 13 OF 36 CAPLUS COPYRIGHT 2007 ACS on STN

2004:100803 Document No. 140:139483 Method for enhancing the effectiveness of therapies of hyperproliferative diseases. Chang, Yan; Sasak, Vodek (USA). U.S. Pat. Appl. Publ. US 2004023925 A1 20040205, 14 pp., Cont.-in-part of U.S. Ser. No. 176,235. (English). CODEN: USXXCO. APPLICATION: US 2003-408723 20030407. PRIORITY: US 2001-299991P 20010621; US 2002-176235 20020620.

AB The efficacy of conventional cancer therapies such as surgery, chemotherapy and radiation is enhanced by the use of a therapeutic material which binds to and interacts with galectins. The therapeutic material can enhance apoptosis thereby increasing the effectiveness of oncolytic agents. It can also **inhibit** angiogenesis thereby moderating tumor growth and/or metastasis.

L19 ANSWER 14 OF 36 CAPLUS COPYRIGHT 2007 ACS on STN

2004:59563 Document No. 140:122766 Treatment of cancer with anti-**ErbB2 antibodies.** Kelsey, Stephen M.; Sliwkowski, Mark X. (Genentech, Inc., USA). U.S. Pat. Appl. Publ. US 2004013667 A1 20040122, 56 pp., Cont.-in-part of U.S. Ser. No. 268,501. (English).

CODEN: USXXCO. APPLICATION: US 2003-608626 20030627. PRIORITY: US 1999-141316P 19990625; US 2000-602812 20000623; US 2002-268501 20021010.

AB The present application describes methods for treating cancer with anti-**ErbB2 antibodies**, such as anti-**ErbB2 antibodies** that block ligand activation of an ErbB receptor. Recombinant humanized monoclonal **antibody** 2C4 was effective in **inhibiting** breast cancer tumor growth in mice with MCF7 xenografts.

L19 ANSWER 15 OF 36 MEDLINE on STN

2004426376. PubMed ID: 15254267. Autocrine extracellular signal-regulated kinase (ERK) activation in normal human keratinocytes: metalloproteinase-mediated release of amphiregulin triggers signaling from ErbB1 to ERK. Kansra Sanjay; Stoll Stefan W; Johnson Jessica L; Elder James T. (Departments of Dermatology, University of Michigan Medical Center, Ann Arbor, MI 48109, USA.. sanjay.kansra@uc.edu) . Molecular biology of the cell, (2004 Sep) Vol. 15, No. 9, pp. 4299-309. Electronic Publication: 2004-07-14. Journal code: 9201390. ISSN: 1059-1524. Pub. country: United States. Language: English.

AB ErbB signaling through extracellular signal-regulated kinase (ERK) has been implicated in regulating the expression of ErbB ligands in hyperproliferative skin disorders and wound healing. Here, we characterize the process of autocrine ERK activation in cultured normal human keratinocytes (NHKs) subjected to growth factor (GF) deprivation. Basal ERK phosphorylation was lower after 48 h than after 24 h of GF deprivation, and lowest at 30-60 min after an additional medium change. ERK phosphorylation was markedly increased by low concentrations of epidermal growth factor (EGF) (0.2-1 ng/ml) that provoked only a limited increase in ErbB1 tyrosine phosphorylation and internalization. Basal ErbB tyrosine phosphorylation and ERK phosphorylation were **inhibited** by two different ErbB receptor tyrosine kinase **inhibitors**, by the ErbB1-specific neutralizing monoclonal **antibody** 225 IgG, by two different metalloproteinase **inhibitors**, and by neutralizing **antibodies** against amphiregulin (AR). In contrast, these responses were unaffected by neutralizing **antibodies** against other ErbB1 ligands or the **ErbB2 inhibitors** geldanamycin and AG825. The time course of autocrine ERK phosphorylation correlated with the appearance of soluble AR, and two different metalloproteinase **inhibitors** blocked AR release. These results define an amphiregulin- and ErbB1-dependent mechanism by which autocrine ERK activation is maintained in NHKs, even when ErbB1 autophosphorylation and internalization are limited.

L19 ANSWER 16 OF 36 MEDLINE on STN

2004584558. PubMed ID: 15557433. Role of **ErbB2** in Corneal Epithelial Wound Healing. Xu Ke-Ping; Riggs April; Ding Yu; Yu Fu-Shin X. (Department of Cellular Biology and Anatomy, Medical College of Georgia, Augusta, Georgia.) Investigative ophthalmology & visual science, (2004 Dec) Vol. 45, No. 12, pp. 4277-83. Journal code: 7703701. ISSN: 0146-0404. Pub. country: United States. Language: English.

AB PURPOSE: Human corneal epithelial cells (HCECs) were functionally depleted of **erbB2** to elucidate its role in epidermal growth factor (EGF) receptor (EGFR) activation-dependent cell migration. METHODS: The retrovirus pBabe-5R, which encodes an **erbB2** single-chain **antibody** with an endoplasmic reticulum (ER)-targeting sequence, and control pBabe-puro were used to infect THCE cells (an SV40-immortalized HCEC line). Several cell lines expressing 5R were selected along with a pBabe-puro control line. The depletion of **erbB2** was verified by cell surface biotinylation of proteins, followed by streptavidin precipitation and subsequent detection of **erbB2** by immunoblot analysis. Activation of erbBs was analyzed by immunoprecipitation using the phosphotyrosine **antibody** pY20, followed by Western blot analysis with erbB1 or **erbB2** **antibodies.** Phosphorylation of extracellular signal-regulated

kinase (ERK) and phosphatidylinositol 3'-kinase (PI3K) was analyzed by Western blot with **antibodies** specific to phosphorylated proteins. Effects of **erbB2** depletion on heparin-binding EGF-like growth factor (HB-EGF)-induced cell migration were determined by Boyden chamber migration assay and by scratch wound assay. RESULTS: Wounding induced **erbB2** tyrosine phosphorylation. Expression of 5R encoding an **erbB2** single-chain **antibody** with an endoplasmic reticulum-targeting sequence depleted the cell surface expression of **erbB2** in HCECs. Wounding resulted in a rapid increase in the phosphorylation of erbB1 in both 5R-expressing and control cells, whereas wound-induced **erbB2** phosphorylation in 5R-expressing cells was not detectable. Depletion of functional **erbB2** attenuated the healing of scratch wounds in the presence of HB-EGF and impaired both chemotactic migration stimulated by HB-EGF and haptotactic migration toward a fibronectin-collagen I (3:1; FNC) coating mix. Expression of 5R affected both the intensity and the duration of wound-induced, EGFR-elicited ERK and PI3K activation. **Inhibition** of ERK and PI3K pathways in cultured porcine corneas impaired ex vivo epithelial wound healing. CONCLUSIONS: **ErbB2** serves as a critical component that couples erbB receptor tyrosine kinase to the migration machinery of corneal epithelial cells.

L19 ANSWER 17 OF 36 MEDLINE on STN DUPLICATE 1
2004165913. PubMed ID: 15059917. Blockade of epidermal growth factor- or heregulin-dependent **ErbB2** activation with the anti-**ErbB2** monoclonal **antibody** 2C4 has divergent downstream signaling and growth effects. Jackson James G; St Clair Patricia; Sliwkowski Mark X; Brattain Michael G. (Department of Surgery, University of Texas Health Science Center, San Antonio, Texas, USA.) Cancer research, (2004 Apr 1) Vol. 64, No. 7, pp. 2601-9. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB Due to heterodimerization and a variety of stimulating ligands, the ErbB receptor system is both diverse and flexible, which proves particularly advantageous to the aberrant signaling of cancer cells. However, specific mechanisms of how a particular receptor contributes to generating the flexibility that leads to aberrant growth regulation have not been well described. We compared the utilization of **ErbB2** in response to epidermal growth factor (EGF) and heregulin stimulation in colon carcinoma cells. Anti-**ErbB2** monoclonal **antibody** 2C4 blocked heregulin-stimulated phosphorylation of **ErbB2** and ErbB3; activation of mitogen-activated protein kinase (MAPK), phosphatidylinositol 3'-kinase (PI3K), and Akt; proliferation; and anchorage-independent growth. 2C4 blocked EGF-mediated phosphorylation of **ErbB2** and **inhibited** PI3K/Akt and anchorage-independent growth but did not affect ErbB1 or MAPK. Immunoprecipitations showed that ErbB3 and Grb2-associated binder (Gab) 1 were phosphorylated and associated with PI3K activity after heregulin treatment and that Gab1 and Gab2, but not ErbB3, were phosphorylated and associated with PI3K activity after EGF treatment. These data show that monoclonal **antibody** 2C4 **inhibited** all aspects of heregulin signaling as well as anchorage-independent and monolayer growth. Furthermore, we identify **ErbB2** as a critical component of EGF signaling to the Gab1/Gab2-PI3K-Akt pathway and anchorage-independent growth, but EGF stimulation of MAPK and monolayer growth can occur efficiently without the contribution of **ErbB2.**

L19 ANSWER 18 OF 36 MEDLINE on STN DUPLICATE 2
2004069870. PubMed ID: 14871842. **Antibodies** directed against Lewis-Y antigen **inhibit** signaling of Lewis-Y modified ErbB receptors. Klinger Markus; Farhan Hesso; Just Herwig; Drobny Helmut; Himmler Gottfried; Loibner Hans; Mudde Geert C; Freissmuth Michael; Sexl Veronika. (Department of Surgery, University of Vienna, Vienna, Austria.) Cancer research, (2004 Feb 1) Vol. 64, No. 3, pp. 1087-93. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB The majority of cancer cells derived from epithelial tissue express

Lewis-Y (LeY) type difucosylated oligosaccharides on their plasma membrane. This results in the modification of cell surface receptors by the LeY antigen. We used the epidermal growth factor (EGF) receptor family members ErbB1 and **ErbB2** as model systems to investigate whether the sugar moiety can be exploited to block signaling by growth factor receptors in human tumor cells (i.e., SKBR-3 and A431, derived from a breast cancer and a vulval carcinoma, respectively). The monoclonal anti-LeY **antibody** ABL364 and its humanized version IGN311 immunoprecipitated ErbB1 and **ErbB2** from detergent lysates of A431 and SKBR-3, respectively. ABL364 and IGN311 blocked EGF- and heregulin-stimulated phosphorylation of mitogen-activated protein kinase [MAPK = extracellular signal-regulated kinase 1/2] in SKBR-3 and A431 cells. The effect was comparable in magnitude with that of trastuzumab (Herceptin) and apparently noncompetitive with respect to EGF. Stimulation of MAPK by ErbB was dynamin dependent and contingent on receptor internalization. ABL364 and IGN311 changed the intracellular localization of fluorescent EGF-containing endosomes and accelerated recycling of intracellular [(125)I]EGF to the plasma membrane. Taken together, these observations show that **antibodies** directed against carbohydrate side chains of ErbB receptors are capable of **inhibiting** ErbB-mediated signaling. The ability of these **antibodies** to reroute receptor trafficking provides a mechanistic explanation for their **inhibitory** action.

L19 ANSWER 19 OF 36 MEDLINE on STN

2004001993. PubMed ID: 14697248. Overexpression of **ErbB2** receptor **inhibits** IGF-I-induced Shc-MAPK signaling pathway in breast cancer cells. Lu Yuhong; Zi Xiaolin; Zhao Yunhua; Pollak Michael. (Division of Experimental Medicine, Department of Medicine and Department of Oncology, McGill University, Montreal, Que, Canada.) Biochemical and biophysical research communications, (2004 Jan 16) Vol. 313, No. 3, pp. 709-15. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB Overexpression of the **ErbB2** receptor in one-third of human breast cancers contributes to the transformation of epithelial cells and predicts poor prognosis for breast cancer patients. We report that the overexpression of **ErbB2 inhibits** IGF-I-induced MAPK signaling. IGF-I-induced MAPK phosphorylation and MAPK kinase activity are reduced in **ErbB2** overexpressing MCF-7/HER2-18 cells relative to control MCF-7/neo cells. In SKBR3/IGF-IR cells, reduction of **ErbB2** by antisense methodology restores the IGF-I-induced MAPK activation. The **inhibition** of IGF-I-induced **MAP kinase** activation in **ErbB2** overexpressing breast cancer cells is correlated with decreased IGF-I-induced Shc tyrosine-phosphorylation, leading to a decreased association of Grb2 with Shc and decreased Raf phosphorylation. However, IGF-I-induced tyrosine-phosphorylation of IGF-I receptor and IRS-I and AKT phosphorylation were unaffected by **ErbB2** overexpression. Consistent with these results, we observed that the proportion of IGF-I-stimulated proliferation blocked by the MAPK **inhibitor** PD98059 fell from 82.6% in MCF-7/neo cells to 41.2% in MCF-7/HER2-18 cells. These data provide evidence for interplay between the IGF-IR and **ErbB2** signaling pathways. They are consistent with the view that the IGF-IR mediated attenuation of trastuzumab-induced growth **inhibition** we recently described is dependent on IGF-I-induced PI3K signaling rather than IGF-I-induced MAPK signaling.

L19 ANSWER 20 OF 36 MEDLINE on STN DUPLICATE 3

2004451979. PubMed ID: 15358191. Cytotoxicity of the novel anti-cancer drug rViscumin depends on HER-2 levels in SKOV-3 cells. Abuharbeid Shaker; Apel Jurgen; Sander Martin; Fiedler Babette; Langer Martin; Zuzarte Mary-Lou; Czubayko Frank; Aigner Achim. (Department of Pharmacology and Toxicology, Philipps-University School of Medicine, Marburg, Germany.) Biochemical and biophysical research communications, (2004 Aug 20) Vol. 321, No. 2, pp. 403-12. Journal code: 0372516. ISSN: 0006-291X. Pub.

country: United States. Language: English.

AB rViscumin is a recombinant mistletoe lectin under clinical investigation as new anti-cancer drug. The relationship between oncogene, e.g., HER-2/neu (c-**erbB2**) receptor activation and tumor cell chemosensitivity, is of considerable importance to better predict the response to chemotherapy. Here, we analyze the cellular and molecular effects of HER-2 expression on rViscumin chemotoxicity in SKOV-3 cells. We show that selective depletion of HER-2 by ribozyme-targeting markedly decreases cellular sensitivity towards rViscumin. These findings are confirmed by treatment with the well-established **inhibitory** HER-2 **antibody** trastuzumab (Herceptin). Using clonal ribozyme-transfected cell lines, we establish a 'HER-2 gene dose' dependence of rViscumin cytotoxicity, which is due to differential induction of apoptosis and is not mediated by cell cycle alterations or altered cellular rViscumin binding/internalization. We further demonstrate an rViscumin-mediated, HER-2-dependent down-regulation of bcl-2 and the dose-dependent activation of members of the MAPK family, p42/44, SAPK/JNK, and p38, but not of caspases-3 and -7.

L19 ANSWER 21 OF 36 CAPLUS COPYRIGHT 2007 ACS on STN

2003:870117 Document No. 140:174621 Herstatin **inhibits** heregulin-mediated breast cancer cell growth and overcomes tamoxifen resistance in breast cancer cells that overexpress HER-2. Jhabvala-Romero, Farida; Evans, Adam; Guo, Shuhua; Denton, Michael; Clinton, Gail Mary (Department of Biochemistry and Molecular Biology, Oregon Health and Science University, Portland, OR, 97239-3098, USA). Oncogene, 22(50), 8178-8186 (English) 2003. CODEN: ONCNES. ISSN: 0950-9232. Publisher: Nature Publishing Group.

AB Ligands of the ErbB family of receptors and estrogens control the proliferation of breast cancer cells. Overexpression of human EGF receptor HER-2 (**erbB2**) leads to amplified heregulin (HRG) signaling, promoting more aggressive breast cancer that is nonresponsive to estrogen and the antiestrogenic drug tamoxifen. Herstatin (Hst), a secreted HER-2 gene product, binds to the HER-2 receptor ectodomain blocking receptor activation. The aim of this study was to investigate the impact of this HER-2 **inhibitor** on HRG-induced signaling, proliferation, and sensitivity to tamoxifen in breast cancer cells with and without HER-2 overexpression. The expression of Hst in MCF7 cells eliminated HRG signaling through both mitogen-activated protein kinase and Akt pathways and prevented HRG-mediated proliferation. The loss in signaling corresponded to downregulation of the HRG receptors, HER-3 and HER-4, whereas HER-2 overexpression strongly stimulated the levels of both HRG receptors. Although Hst blocked HRG signaling in both parental and HER-2 transfected cells, it enhanced sensitivity to tamoxifen only in the MCF7 cells that overexpressed HER-2. To evaluate further the efficacy of Hst as an anticancer agent, His-tagged Hst was expressed in transfected insect cells, purified, and added to the breast cancer cells. As in the transfected cells, purified Hst **inhibited** HER-3 levels and suppressed HRG-induced proliferation of MCF7 and BT474 breast cancer cells. In contrast, the HER-2 monoclonal **antibody**, herceptin, downregulated HER-2, but not HER-3. These results suggest the potential use of Hst against HRG-mediated growth of breast cancers with high and low levels of HER-2 and against tamoxifen resistance in HER-2 overexpressing breast cancer.

L19 ANSWER 22 OF 36 MEDLINE on STN DUPLICATE 4

2003324220. PubMed ID: 12853971. NIK is a component of the EGF/heregulin receptor signaling complexes. Chen Danying; Xu Liang-Guo; Chen Lei; Li Lixia; Zhai Zhonghe; Shu Hong-Bing. (Department of Cell Biology and Genetics, College of Life Sciences, Peking University, Beijing 100871, China.) Oncogene, (2003 Jul 10) Vol. 22, No. 28, pp. 4348-55. Journal code: 8711562. ISSN: 0950-9232. Pub. country: England: United Kingdom. Language: English.

AB Nuclear factor kappaB-inducing kinase (NIK) is a member of the **MAP kinase** kinase kinase family that was first identified as a

component of the TNF-R1-induced NF-kappaB activation pathway (TNF, tumor necrosis factor; nuclear factor kappaB, NF-kappaB). Gene knockout study, however, suggests that NIK is dispensable for TNF-R1- but required for lymphotoxin-beta receptor-induced NF-kappaB activation. A NIK kinase inactive mutant is a potent **inhibitor** of NF-kappaB activation triggered by various stimuli, suggesting that NIK is involved in a broad range of NF-kappaB activation pathways. To unambiguously identify signaling pathways that NIK participates in, we screened **antibody** arrays for proteins that are associated with NIK. This effort identified ErbB4, one of the EGF/heregulin receptors, and Grb7, an adapter protein associated with ErbB4 (ErbB, epidermal growth factor receptor family protein; EGF, epidermal growth factor; Grb, growth factor receptor bound). Coimmunoprecipitation experiments demonstrated that NIK interacted with Grb7, as well as Grb10 and Grb14, but not Grb2. Domain mapping experiments indicated that the central GM domain of Grb7 was sufficient for its interaction with NIK. Coimmunoprecipitation experiments also indicated that Grb7 and NIK could be simultaneously recruited into signaling complexes of all known EGF/heregulin receptors, including EGFR, **ErbB2**, ErbB3, and ErbB4. In reporter gene assays, NIK could potentiate Grb7, **ErbB2**/ErbB4, and EGF-induced NF-kappaB activation. A NIK kinase inactive mutant could block **ErbB2** /ErbB4 and EGF-induced NF-kappaB activation. Moreover, EGF/heregulin receptors activated NF-kappaB in wild-type, but not NIK-/- embryonic fibroblasts. Our findings suggest that NIK is a component of the EGF/heregulin receptor signaling complexes and involved in NF-kappaB activation triggered by these receptors.

L19 ANSWER 23 OF 36 CAPLUS COPYRIGHT 2007 ACS on STN
2003:79547 Document No. 138:269485 Heregulin induces transcriptional activation of the progesterone receptor by a mechanism that requires functional ErbB-2 and mitogen-activated protein kinase activation in breast cancer cells. Labriola, Leticia; Salatino, Mariana; Proietti, Cecilia J.; Pecci, Adali; Coso, Omar A.; Kornblihtt, Alberto R.; Charreau, Eduardo H.; Elizalde, Patricia V. (Instituto de Biologia y Medicina Experimental, Buenos Aires, 1428, Argent.). Molecular and Cellular Biology, 23(3), 1095-1111 (English) 2003. CODEN: MCEBD4. ISSN: 0270-7306. Publisher: American Society for Microbiology.
AB The present study addresses the capacity of heregulin (HRG), a ligand of type I receptor tyrosine kinases, to transactivate the progesterone receptor (PR). For this purpose, we studied, on the one hand, an exptl. model of hormonal carcinogenesis in which the synthetic progestin medroxyprogesterone acetate (MPA) induced mammary adenocarcinomas in female BALB/c mice and, on the other hand, the human breast cancer cell line T47D. HRG was able to exquisitely regulate biochem. attributes of PR in a way that mimicked PR activation by progestins. Thus, HRG treatment of primary cultures of epithelial cells of the progestin-dependent C4HD murine mammary tumor line and of T47D cells induced a decrease of protein levels of PRA and -B isoforms and the downregulation of progesterone-binding sites. HRG also promoted a significant increase in the percentage of PR localized in the nucleus in both cell types. DNA mobility shift assay revealed that HRG was able to induce PR binding to a progesterone response element (PRE) in C4HD and T47D cells. Transient transfections of C4HD and T47D cells with a plasmid containing a PRE upstream of a chloramphenicol acetyltransferase (CAT) gene demonstrated that HRG promoted a significant increase in CAT activity. In order to assess the mol. mechanisms underlying PR transactivation by HRG, we blocked ErbB-2 expression in C4HD and T47D cells by using antisense oligodeoxynucleotides to ErbB-2 mRNA, which resulted in the abolishment of HRG's capacity to induce PR binding to a PRE, as well as CAT activity in the transient-transfection assays. Although the **inhibition** of HRG binding to ErbB-3 by an anti-ErbB-3 monoclonal **antibody** suppressed HRG-induced PR activation, the abolishment of HRG binding to ErbB-4 had no effect on HRG activation of PR. To investigate the role of mitogen-activated protein kinases (MAPKs), we used the selective MEK1/MAPK **inhibitor** PD98059. Blockage of MAPK activation resulted in

complete abrogation of HRG's capacity to induce PR binding to a PRE, as well as CAT activity. Finally, we demonstrate here for the first time that HRG-activated MAPK can phosphorylate both human and mouse PR in vitro.

L19 ANSWER 24 OF 36 MEDLINE on STN
2004076820. PubMed ID: 14965445. A unique model system for tumor progression in GBM comprising two developed human neuro-epithelial cell lines with differential transforming potential and coexpressing neuronal and glial markers. Shiras Anjali; Bhosale Arti; Shepal Varsha; Shukla Ravi; Baburao V S; Prabhakara K; Shastry Padma. (National Centre for Cell Science, NCCS Complex, Ganeshkhind, Pune, India.. anjalishiras@nccs.res.in) . Neoplasia (New York, N.Y.), (2003 Nov-Dec) Vol. 5, No. 6, pp. 520-32. Journal code: 100886622. ISSN: 1522-8002. Pub. country: United States. Language: English.
AB The molecular mechanisms involved in tumor progression from a low-grade astrocytoma to the most malignant glioblastoma multiforme (GBM) have been hampered due to lack of suitable experimental models. We have established a model of tumor progression comprising of two cell lines derived from the same astrocytoma tumor with a set of features corresponding to low-grade glioma (as in HNGC-1) and high-grade GBM (as in HNGC-2). The HNGC-1 cell line is slow-growing, contact-**inhibited**, nontumorigenic, and noninvasive, whereas HNGC-2 is a rapidly proliferating, anchorage-independent, highly tumorigenic, and invasive cell line. The proliferation of cell lines is independent of the addition of exogenous growth factors. Interestingly, the HNGC-2 cell line displays a near-haploid karyotype except for a disomy of chromosome 2. The two cell lines express the neuronal precursor and progenitor markers vimentin, nestin, MAP-2, and NFP160, as well as glial differentiation protein S100beta. The HNGC-1 cell line also expresses markers of mature neurons like Tuj1 and GFAP, an astrocytic differentiation marker, hence contributing toward a more morphologically differentiated phenotype with a propensity for neural differentiation in vitro. Additionally, overexpression of epidermal growth factor receptor and c-**erbB2**, and loss of fibronectin were observed only in the HNGC-2 cell line, implicating the significance of these pathways in tumor progression. This in vitro model system assumes importance in unraveling the cellular and molecular mechanisms in differentiation, transformation, and gliomagenesis.

L19 ANSWER 25 OF 36 MEDLINE on STN DUPLICATE 5
2002424713. PubMed ID: 12181354. c-**erbB2**-induced disruption of matrix adhesion and morphogenesis reveals a novel role for protein kinase B as a negative regulator of alpha(2)beta(1) integrin function. Lindberg Lachmi E; Hedjazifar Shahram; Baeckstrom Dan. (Department of Medical Biochemistry, University of Goteborg, Sweden.) Molecular biology of the cell, (2002 Aug) Vol. 13, No. 8, pp. 2894-908. Journal code: 9201390. ISSN: 1059-1524. Pub. country: United States. Language: English.
AB Overexpression of the growth factor receptor subunit c-**erbB2**, leading to its ligand-independent homodimerization and activation, has been implicated in the pathogenesis of mammary carcinoma. Here, we have examined the effects of c-**erbB2** on the adhesive properties of a mammary epithelial cell line, HB2/tnz34, in which c-**erbB2** homodimerization can be induced by means of a transfected hybrid "trk-neu" construct. trk-neu consists of the extracellular domain of the trkA nerve growth factor (NGF) receptor fused to the transmembrane and cytoplasmic domains of c-**erbB2**, allowing NGF-induced c-**erbB2** homodimer signaling. Both spreading and adhesion on collagen surfaces were impaired on c-**erbB2** activation in HB2/tnz34 cells. **Antibody**-mediated stimulation of alpha(2)beta(1) integrin function restored adhesion, suggesting a direct role for c-**erbB2** in integrin inactivation. Using pharmacological **inhibitors** and transient transfections, we identified signaling pathways required for suppression of integrin function by c-**erbB2**. Among these was the MEK-ERK pathway, previously implicated in integrin inactivation.

However, we could also show that downstream of phosphoinositide-3-kinase (PI3K), protein kinase B (PKB) acted as a previously unknown, potent **inhibitor** of integrin function and mediator of the disruptive effects of c-**erbB2** on adhesion and morphogenesis. The integrin-linked kinase, previously identified as a PKB coactivator, was also found to be required for integrin inactivation by c-**erbB2**. In addition, the PI3K-dependent mTOR/S6 kinase pathway was shown to mediate c-**erbB2**-induced **inhibition** of adhesion (but not spreading) independently of PKB. Overexpression of MEK1 or PKB suppressed adhesion without requirement for c-**erbB2** activation, suggesting that these two pathways partake in integrin **inhibition** by targeting common downstream effectors. These results demonstrate a major novel role for PI3K and PKB in regulation of integrin function.

L19 ANSWER 26 OF 36 MEDLINE on STN

2002065871. PubMed ID: 11791178. Autocrine heregulin generates growth factor independence and blocks apoptosis in colon cancer cells. Venkateswarlu Srinivas; Dawson Dawn M; St Clair Patricia; Gupta Anjana; Willson James K V; Brattain Michael G. (Department of Surgery, University of Texas Health Science Center at San Antonio, Texas, TX 78284, USA.) Oncogene, (2002 Jan 3) Vol. 21, No. 1, pp. 78-86. Journal code: 8711562. ISSN: 0950-9232. Pub. country: England: United Kingdom. Language: English.

AB The aim of this study was to determine whether constitutive **ErbB2** activation controls growth and apoptosis in colon cancer cells. Growth arrested GEO cells showed constitutive activation of **ErbB2** in the absence of exogenous growth factors or serum supplementation. Higher levels of heregulin and **ErbB2** activation were observed in the growth-arrested state and cell cycle re-entry was independent of exogenous growth factors. Blockade of **ErbB2** activation by heregulin neutralizing **antibodies** and by AG879 resulted in prevention of cell cycle re-entry. This indicated that autocrine heregulin activity was responsible for growth factor independence and for cell cycle re-entry. Activation of **ErbB2** was the result of heregulin mediated interaction with ErbB3 and generated downstream activation of the ERK and the PI3K/AKT pathways. Heregulin neutralizing **antibody** treatment of growth arrested GEO cells also generated apoptosis as reflected by PARP cleavage and DNA fragmentation indicating a cell survival signal was also induced by the constitutively activated **ErbB2**. The activation of AKT but not the MAPK pathway was responsible for cell survival in these cells.

L19 ANSWER 27 OF 36 CAPLUS COPYRIGHT 2007 ACS on STN

2001:677067 Document No. 135:251931 Function homology screening method, and use in identification of drug candidates. Berg, Ellen L.; Butcher, Eugene C.; Melrose, Jennifer; Plavec, Ivan (Bioseek, Inc., USA). PCT Int. Appl. WO 2001067103 A1 20010913, 128 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US7190 20010306. PRIORITY: US 2000-PV186976 20000306; US 2000-PV195672 20000407.

AB A method is provided for screening biol. active agents based on the anal. of complex biol. responses in culture. Methods for selecting cells and culture conditions for such screens are provided, as well as the identification of an optimized set of discrete parameters to be measured, and the use of biomap anal. for rapid identification and characterization of drug candidates, genetic sequences acting pathways, and the like. A feature of the invention is simultaneous screening of a large number of cellular pathways, and the rapid identification of compds. that cause cellular responses.

L19 ANSWER 28 OF 36 MEDLINE on STN DUPLICATE 6

2001184239. PubMed ID: 11245489. Up-regulation of vascular endothelial growth factor in breast cancer cells by the heregulin-beta1-activated p38 signaling pathway enhances endothelial cell migration. Xiong S; Grijalva R; Zhang L; Nguyen N T; Pisters P W; Pollock R E; Yu D. (Department of Surgical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston 77030, USA.) Cancer research, (2001 Feb 15) Vol. 61, No. 4, pp. 1727-32. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB Heregulin (HRG) belongs to a family of polypeptide growth factors that bind to receptor tyrosine kinases ErbB3 and ErbB4. HRG binding induces ErbB3 and ErbB4 heterodimerization with **ErbB2**, activating downstream signal transduction. Vascular endothelial growth factor (VEGF) is a primary regulator of physiological angiogenesis and is a major mediator of pathological angiogenesis, such as tumor-associated neovascularization. In this study, we demonstrate that HRG-beta1 increased secretion of VEGF from breast cancer cells in a time- and dosage-dependent manner and that this increase resulted from up-regulation of VEGF mRNA expression via transcriptional activation of the VEGF promoter. Deletion and mutational analysis revealed that a CA-rich upstream HRG response element located between nucleotide-2249 and -2242 in the VEGF promoter mediated HRG-induced transcriptional up-regulation of VEGF. While investigating the downstream signaling pathways involved in HRG-mediated up-regulation of VEGF, we found that HRG activated extracellular signal-regulated protein kinases, Akt kinase, and p38 mitogen-activated protein kinase (MAPK). However, only the specific **inhibitor** of p38 MAPK (SB203580), not extracellular signal-regulated kinase **inhibitor** PD98059 nor the **inhibitor** of phosphatidylinositol 3-kinase-Akt pathway (Wortmannin), blocked the up-regulation of VEGF by HRG. The HRG-stimulated secretion of VEGF from breast cancer cells resulted in increased migration of murine lung endothelial cells, an activity that was **inhibited** by either VEGF-neutralizing **antibody** or SB203580. These results show that HRG can activate p38 MAPK to enhance VEGF transcription via an upstream HRG response element, leading to increased VEGF secretion and angiogenic response in breast cancer cells.

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2001:547210 Document No.: PREV200100547210. ErbB receptor activation increases survival of human glioma cells. Ritch, P. S. [Reprint author]; Sontheimer, H. W. [Reprint author]. Neurobiol Dept, Univ Alabama Birmingham, Birmingham, AL, USA. Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1, pp. 1242. print.
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience. San Diego, California, USA. November 10-15, 2001.
ISSN: 0190-5295. Language: English.

AB Expression of erbB receptors has been associated with increased aggressiveness and decreased patient survival in a number of human malignancies including glioblastoma. Despite evidence demonstrating an inverse relationship between erbB receptor expression and disease progression in human gliomas, relatively little is known regarding the role of these receptors in glioma cell biology. Previous studies implicate activation of the Akt-survival pathway downstream of erbB receptor autophosphorylation. This pathway is dependent on PI-3 kinase and increases survival by phosphorylating and inactivating pro-apoptotic regulators such as BAD. In this study, we set out to examine whether the stimulation of erbB receptors by neuregulin could increase the survival of glioma cells by activating the Akt-survival cascade. Expression of neuregulin receptors was confirmed using western blot analysis and immunocytochemistry in a panel of human glioma cell lines encompassing both WHO grades III and IV. Recombinant beta1-neuregulin induced tyrosine phosphorylation of **erbB2** and erbB3 receptors in a dose and time dependent manner. Activation of the Akt pathway was demonstrated immunocytochemically using **antibodies** specific for phospho-Akt.

Akt phosphorylation could be **inhibited** by the PI-3 kinase **inhibitor** LY294002 but not by the **MAP kinase inhibitor** PD98059. The functional consequence of Akt activation by neuregulin was examined using two separate survival assays. The overall cell number was increased in a dose dependent manner and was **inhibited** by LY294002. These findings indicate that erbB receptor activation can induce Akt-survival events in human glioma cells.

L19 ANSWER 30 OF 36 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN

2001:900590 The Genuine Article (R) Number: 489DA. ZD1839 (Iressa), a novel epidermal growth factor receptor (EGFR) tyrosine kinase **inhibitor**, potently **inhibits** the growth of EGFR-positive cancer cell lines with or without **erbB2** overexpression. Anderson N G (Reprint); Ahmad T; Chan K; Dobson R; Bundred N J. Univ Manchester, Sch Biol Sci, Oxford Rd, Manchester M13 9PT, Lancs, England (Reprint); Univ Manchester, Sch Biol Sci, Manchester M13 9PT, Lancs, England; Univ Manchester, Sch Med, Dept Surg, Div Canc Studies, Manchester M13 9PT, Lancs, England. INTERNATIONAL JOURNAL OF CANCER (15 DEC 2001) Vol. 94, No. 6, pp. 774-782. ISSN: 0020-7136. Publisher: WILEY-LISS, DIV JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012 USA. Language: English. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Overexpression of the growth factor receptors EGFR and **erbB2** occurs frequently in several human cancers and is associated with aggressive tumour behaviour and poor patient prognosis. We have investigated the effects of ZD1839 (Iressa), a novel EGFR tyrosine kinase **inhibitor**, on the growth, in vitro and in vivo, of human cancer cell lines expressing various levels of EGFR and **erbB2.** Proliferation of EGFR-overexpressing A431 and MDA-MB-231 cells in vitro was potently **inhibited** (50%-70%) by ZD1839 with half-maximally effective doses in the low nanomolar range. In parallel, ZD1839 blocked autophosphorylation of EGFR and prevented activation of PLC-gammaI, ERK **MAP kinases** and PKB/Akt by EGF. It also **inhibited** proliferation in EGFR(+) cancer cell lines overexpressing **erbB2** (SKBr3, SKOV3, BT474) by between 20% and 80%, effects which correlated with **inhibition** of EGF-dependent **erbB2** phosphorylation and activation of ERK **MAP kinase** and PKB/Akt in SKOV3 cells. Oral administration of ZD1839 **inhibited** the growth of MDA-MB-231 and SKOV3 tumours, established as xenografts in athymic mice, by 71% and 32%, respectively. Growth **inhibition** coincided with reduced proliferation but no change in apoptotic index. Collectively, these results show that ZD1839, at the doses studied, is a potent **inhibitor** of proliferation not only in cells overexpressing EGFR but also in EGFR(+) cells that overexpress **erbB2.** (C) 2001 Wiley-Liss, Inc.

L19 ANSWER 31 OF 36 CAPLUS COPYRIGHT 2007 ACS on STN

2000:788065 Document No. 134:54702 Constitutive tyrosine phosphorylation of ErbB-2 via Jak2 by autocrine secretion of prolactin in human breast cancer. Yamauchi, Toshimasa; Yamauchi, Naoko; Ueki, Kohjiro; Sugiyama, Takuya; Waki, Hironori; Miki, Hiroshi; Tobe, Kazuyuki; Matsuda, Satoru; Tsushima, Toshio; Yamamoto, Tadashi; Fujita, Toshiro; Taketani, Yuji; Fukayama, Masashi; Kimura, Satoshi; Yazaki, Yoshio; Nagai, Ryozo; Kadowaki, Takashi (Department of Internal Medicine, Graduate School of Medicine, University of Tokyo, Tokyo, 113, Japan). Journal of Biological Chemistry, 275(43), 33937-33944 (English) 2000. CODEN: JBCHA3. ISSN: 0021-9258. Publisher: American Society for Biochemistry and Molecular Biology.

AB Overexpression of the oncogene for ErbB-2 is an unfavorable prognostic marker in human breast cancer. Its oncogenic potential appears to depend on the state of tyrosine phosphorylation. However, the mechanisms by which ErbB-2 is constitutively tyrosine-phosphorylated in human breast cancer are poorly understood. We now show that human breast carcinoma samples with ErbB-2 overexpression have higher proliferative and metastatic activity in the presence of autocrine secretion of prolactin

(PRL). By using a neutralizing **antibody** or dominant neg. (DN) strategies or specific **inhibitors**, we also show that activation of Janus kinase Jak2 by autocrine secretion of PRL is one of the significant components of constitutive tyrosine phosphorylation of ErbB-2, its association with Grb2 and activation of mitogen-activated protein (**MAP**) **kinase** in human breast cancer cell lines that overexpress ErbB-2. Furthermore, the neutralizing anti-PRL **antibody** or erbB-2 antisense oligonucleotide or DN Jak2 or Jak2 **inhibitor** or DNRas or **MAP kinase** kinase **inhibitor inhibits** the proliferation of both untreated and PRL-treated cells. Our results indicate that autocrine secretion of PRL stimulates tyrosine phosphorylation of ErbB-2 by Jak2, provides docking sites for Grb2 and stimulates Ras-**MAP kinase** cascade, thereby causing unrestricted cellular proliferation. The identification of this novel cross-talk between ErbB-2 and the autocrine growth stimulatory loop for PRL may provide new targets for therapeutic and preventive intervention of human breast cancer.

L19 ANSWER 32 OF 36 MEDLINE on STN DUPLICATE 7

2000224891. PubMed ID: 10763821. Effects of oncogenic **ErbB2** on G1 cell cycle regulators in breast tumour cells. Neve R M; Sutterluty H; Pullen N; Lane H A; Daly J M; Krek W; Hynes N E. (Friedrich Miescher Institute, Basel, Switzerland.) Oncogene, (2000 Mar 23) Vol. 19, No. 13, pp. 1647-56. Journal code: 8711562. ISSN: 0950-9232. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The **ErbB2** receptor tyrosine kinase is overexpressed in a variety of human tumours. In order to understand the mechanism by which **ErbB2** mediates tumour proliferation we have functionally inactivated the receptor using an intracellularly expressed, ER-targeted single-chain **antibody** (scFV-5R). Inducible expression of scFv-5R in the **ErbB2**-overexpressing SKBr3 breast tumour cell line leads to loss of plasma membrane localized **ErbB2**. Simultaneously, the activity of ErbB3, **MAP kinase** and PKB/Akt decreased dramatically, suggesting that active **ErbB2** /ErbB3 dimers are necessary for sustained activity of these kinases. Loss of functional **ErbB2** caused the SKBr3 tumour cells to accumulate in the G1 phase of the cell cycle. This was a result of reduction in CDK2 activity, which was mediated by a re-distribution of p27Kip1 from sequestering complexes to cyclin E/CDK2 complexes. The level of c-Myc and D-cyclins, proteins involved in p27KiP1 sequestration, decreased in the absence of functional **ErbB2**. Ectopic expression of c-Myc led to an increase in D cyclin levels, CDK2 activity and resulted in a partial G1 rescue. We propose that c-Myc is a primary effector of **ErbB2** -mediated oncogenicity and functions to prevent normal p27Kip1 control of cyclinE/CDK2.

L19 ANSWER 33 OF 36 MEDLINE on STN DUPLICATE 8

2001201412. PubMed ID: 11149601. **Inhibition** of mitogen-activated protein kinase kinase selectively **inhibits** cell proliferation in human breast cancer cells displaying enhanced insulin-like growth factor I-mediated mitogen-activated protein kinase activation. Hermanto U; Zong C S; Wang L H. (Department of Microbiology, Mount Sinai School of Medicine, New York, New York 10029-6574, USA.) Cell growth & differentiation : the molecular biology journal of the American Association for Cancer Research, (2000 Dec) Vol. 11, No. 12, pp. 655-64. Journal code: 9100024. ISSN: 1044-9523. Pub. country: United States. Language: English.

AB Mitogen-activated protein (**MAP**) **kinase** mediates cell proliferation, cell differentiation, and cell survival by regulating signaling pathways activated by receptor protein tyrosine kinases (RPTKs), including the insulin-like growth factor 1 receptor (IGF-IR). We analyzed the upstream signaling components of the **MAP kinase** pathway, including RPTKs, in human breast cancer cell lines and found that some of those components were overexpressed. Importantly, signaling molecules such as IGF-IR, insulin receptor, and insulin receptor substrate 1, leading to the **MAP kinase** pathway, were found to be

concomitantly overexpressed within certain tumor lines, i.e., MCF-7 and T-47D. When compared with the nonmalignant and other breast tumor lines examined, MCF-7 and T-47D cells displayed a more rapid, robust, and sustained **MAP kinase** activation in response to insulin-like growth factor I (IGF-I) stimulation. By contrast, IGF-I treatment led to a sustained down-regulation of **MAP kinase** in those lines overexpressing **ErbB2**-related RPTKs. Interestingly, blocking the **MAP kinase** pathway with PD098059 had the greatest antiproliferative effect on MCF-7 and T-47D among the normal and tumor lines tested. Furthermore, addition of an IGF-IR blocking **antibody** to growth medium attenuated the ability of PD098059 to suppress the growth of MCF-7 and T-47D cells. Thus, our study suggests that concomitant overexpression of multiple signaling components of the IGF-IR pathway leads to the amplification of IGF-I-mediated **MAP kinase** signaling and resultant sensitization to PD098059. The enhanced sensitivity to PD098059 implies an increased requirement for the **MAP kinase** pathway in those breast cancer cells, making this pathway a potential target in the treatment of selected breast malignancies.

L19 ANSWER 34 OF 36 CAPLUS COPYRIGHT 2007 ACS on STN

1999:73931 Document No. 130:232819 1,25-dihydroxyvitamin D3 increases the growth-promoting activity of autocrine epidermal growth factor receptor ligands in keratinocytes. Garach-Jehoshua, Osnat; Ravid, Amiram; Liberman, Uri A.; Koren, Ruth (the Department of Physiology and Pharmacology Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv-Jaffa, 49100, Israel). Endocrinology, 140(2), 713-721 (English) 1999. CODEN: ENDOAO. ISSN: 0013-7227. Publisher: Endocrine Society.

AB Topical treatment of normal skin with 1,25-dihydroxyvitamin D3 [1,25-(OH)2D3] or its synthetic analogs results in enhanced keratinocyte proliferation. Autocrine growth factors belonging to the epidermal growth factor (EGF) family play a major role in controlling keratinocyte proliferation. 1,25-(OH)2D3 enhanced the autonomous proliferation of HaCaT human keratinocytes in the absence of exogenous growth factors. Autonomous and 1,25-(OH)2D3-stimulated proliferations were **inhibited** by a specific **inhibitor** of EGF receptor (EGFR) tyrosine kinase, an EGFR-neutralizing **antibody**, heparin, the heparin antagonist hexadimethrine, and the proteoglycan sulfation **inhibitor** chlorate. These results indicate the involvement of proteoglycan-dependent EGFR ligands. The initial events in EGFR (i.e. ErbB1) mitogenic signal transduction are dimer formation with another ErbB protein and tyrosine cross-phosphorylation. By immunopptn. followed by Western blotting we showed that ErbB1/ErbB3 heterodimers are the major mitogenic signaling entity in 1,25-(OH)2D3-stimulated cells. 1,25-(OH)2D3 did not affect the levels of the proteoglycan-dependent EGFR ligands amphiregulin and heparin-binding EGF nor the synthesis of proteoglycans, as assessed by 35S labeling and ion exchange chromatog. 1,25-(OH)2D3 caused a marked increase in the cellular contents of ErbB1, **ErbB2**, and ErbB3 proteins. The increase in ErbB proteins that mediates signal transduction by EGFR ligands can account for the stimulatory effect of 1,25-(OH)2D3 on autonomous keratinocyte proliferation.

L19 ANSWER 35 OF 36 CAPLUS COPYRIGHT 2007 ACS on STN

1999:425005 Document No. 131:208681 Actinomycin D as a novel SH2 domain ligand **inhibits** Shc/Grb2 interaction in B104-1-1 (neu-transformed NIH3T3) and SAA (hEGFR-overexpressed NIH3T3) cells. Kim, Hyae-Kyeong; Nam, Ji-Youn; Han, Mi Young; Lee, Eun Kyung; Choi, Jung-Do; Bok, Song Hae; Kwon, Byoung-Mog (KIST, Korea Research Institute of Bioscience and Biotechnology, Yusong, Taejon, S. Korea). FEBS Letters, 453(1,2), 174-178 (English) 1999. CODEN: FEBLAL. ISSN: 0014-5793. Publisher: Elsevier Science B.V..

AB Actinomycins, a family of bicyclic chromopeptide lactones with strong antineoplastic activity, were screened as **inhibitors** of Shc/Grb2 interaction in in vitro assay systems. To investigate the effects of actinomycin D on Shc/Grb2 interaction in cell-based expts., we used SAA

(normal hEGFR-overexpressed NIH3T3) cells and B104-1-1 (neu*-transformed NIH3T3) cells, because a large number of the Shc/Grb2 complexes were detected. Associated protein complexes containing Shc were immunopptd. from actinomycin D-treated cell lysates with polyclonal anti-Shc **antibody.** Then the association with Grb2 was assessed by immunoblotting with monoclonal anti-Grb2 **antibody.** The result of the immunoblotting experiment revealed that actinomycin D **inhibited** Shc/Grb2 interaction in a dose-dependent manner in both B104-1-1 and EGF-stimulated SAA cells. The **inhibition** of Shc/Grb2 interaction by actinomycin D in B104-1-1 cells also reduced tyrosine phosphorylation of **MAP kinase** (Erk1/Erk2), one of the major components in the Ras-**MAP kinase** signaling pathway. These results suggest that actinomycin D could be a non-phosphorylated natural and cellular membrane-permeable SH2 domain antagonist.

L19 ANSWER 36 OF 36 CAPLUS COPYRIGHT 2007 ACS on STN
1995:307912 Document No. 122:72669 NDF/heregulin activates **MAP kinase** and p70/p85 S6 kinase during proliferation or differentiation of mammary epithelial cells. Marte, Barbara M.; Graus-Porta, Diana; Jeschke, Margit; Fabbro, Doriano; Hynes, Nancy E.; Taverna, Daniela (Friedrich-Miescher-Institute, Basel, CH-4002, Switz.). Oncogene, 10(1), 167-75 (English) 1995. CODEN: ONCNES. ISSN: 0950-9232. Publisher: Stockton.

AB Neu differentiation factors (NDF) are a novel family of polypeptide factors which activate sub-class I tyrosine kinase receptors. In all mammary epithelial cells analyzed in this study, NDF activates the same signaling pathways while it induces different, cell-specific biol. effects. In AU565 cells which are growth **inhibited**, as well as in T47D or HC11 cells which proliferate in response to NDF, the **MAP kinase** isoforms p44ERK1 and p42ERK2 and the p70/p85 S6 kinase are activated. NDF stimulates tyrosine phosphorylation and the in vitro kinase activity of ErbB-2. When PKC is activated by TPA, NDF is no longer able to activate ErbB-2 in T47D cells, leading to a blockage of cell proliferation. Activation of ErbB-2 by point mutation, or by monoclonal **antibodies**, also stimulates both the MAPK and the p70/p85 S6 kinase pathways. The same monoclonal **antibodies** can induce AU565 cell differentiation. In summary, during growth or differentiation of mammary epithelial cells, NDF stimulates several independent signaling pathways which can also be triggered by ErbB-2 stimulation alone. PKC activation blocks the biol. effect induced by NDF through neg. modulation of ErbB-2.

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=> s psoriasis
L20      95126 PSORIASIS

=> s l20 and MAP kinase
L21        221 L20 AND MAP KINASE

=> s l21 and ErbB receptor
L22          1 L21 AND ERBB RECEPTOR

=> s l21 and ErbB2
L23          1 L21 AND ERBB2

=> dup remove l21
PROCESSING COMPLETED FOR L21
L24        184 DUP REMOVE L21 (37 DUPLICATES REMOVED)

=> s l24 and antagonist
L25         56 L24 AND ANTAGONIST

=> dup remove l25
PROCESSING COMPLETED FOR L25
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L26 56 DUP REMOVE L25 (0 DUPLICATES REMOVED)

=> d l26 1-56 cbib abs

L26 ANSWER 1 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
2007:464184 Document No. 146:455240 Compositions of phosphodiesterase IV inhibitors in combination with other agents, and use thereof for the treatment of autoimmune, inflammatory or allergic conditions. Ray, Abhijit; Dastidar, Sunanda G.; Shirumalla, Rajkumar; Gupta, Suman (Ranbaxy Laboratories Ltd., India). PCT Int. Appl. WO 2007045980 A1 20070426, 138pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2006-IB2931 20061019. PRIORITY: IN 2005-DE2793 20051019.

AB The invention provides pharmaceutical compns. comprising one or more phosphodiesterase IV inhibitors and at least one other active ingredient selected from muscarinic receptor **antagonists**, β2-agonists, p38 **MAP kinase** inhibitors, and corticosteroids, and optionally one or more pharmaceutically acceptable excipients and/or other therapeutic agents. In addition, methods of treating autoimmune, inflammatory or allergic diseases or disorders are provided.

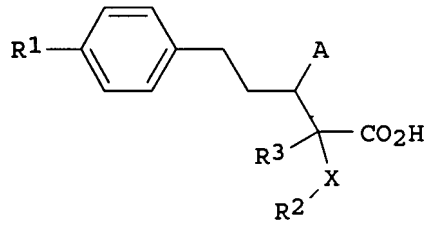
L26 ANSWER 2 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
2007:33392 Document No. 146:141003 Human interleukin 12 subunit p40-binding antibodies, fragments and conjugates in combination with other therapeutic agents for treating IL-12-associated acute and chronic inflammatory disease. Lacy, Susan E.; Fung, Emma; Belk, Jonathan P.; Dixon, Richard W.; Roguska, Michael; Hinton, Paul R.; Kumar, Shankar (Abbott Laboratories, USA). PCT Int. Appl. WO 2007005608 A2 20070111, 211pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2006-US25584 20060629. PRIORITY: US 2005-695679P 20050630.

AB The present invention encompasses IL-12p40 binding proteins, particularly antibodies that bind human interleukin-12 (hIL-12) and/or human IL-23 (hIL-23). Specifically, the invention relates to antibodies that are chimeric, CDR grafted and humanized antibodies. Preferred antibodies have high affinity for hIL-12 and/or hIL-23 and neutralize h IL-12 and/or hIL-23 activity in vitro and in vivo. An antibody of the invention can be a full-length antibody or an antigen-binding portion thereof. Method of making and method of using the antibodies of the invention are also provided. The antibodies, or antibody portions, of the invention are useful for detecting hIL-12 and/or hIL-23 and for inhibiting hIL-12 and/or hIL-23 activity, e.g., in a human subject suffering from a disorder in which hIL-12 and/or hIL-23 activity is detrimental.

L26 ANSWER 3 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
2006:884753 Document No. 145:292717 Preparation of 5-phenylpentanoic acid derivatives as matrix metalloproteinase inhibitors for treating asthma and other inflammatory disorders. Palle, Venkata P.; Sattigeri, Viswajanani Jitendra; Khera, Manoj Kumar; Voleti, Sreedhara Rao; Ray, Abhijit; Dastidar, Sunanda G. (Ranbaxy Laboratories Limited, India). PCT Int. Appl. WO 2006090235 A1 20060831, 94pp. DESIGNATED STATES: W: AE, AG, AL,

AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2006-IB349 20060221. PRIORITY: IN 2005-DE380 20050222.

GI



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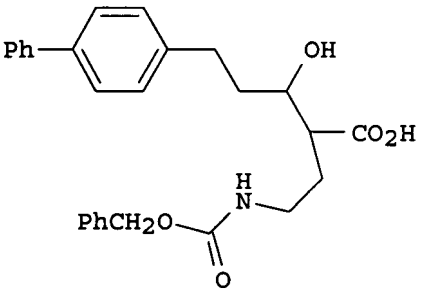

II

AB Title compds. I [X = (CH2)n; n = 1-5; R1 = (un)substituted alk(en/yn)yl, hetero/aryl, etc.; R2 = CO2H and derivs., OH and derivs., (un)substituted alkenyl, aryl, cycloalkyl, etc.; R3 = H, F, ar/cycloalkyl/alkyl; A = OH, alkoxy, NH2, etc.] were prepared as matrix metalloproteinase inhibitors. Thus, reacting tert-Bu 5-(biphenyl-4-yl)-3-oxopentanoate with benzyl aziridine-1-carboxylate, followed by reduction and Boc-deprotection gave acid II. Activities of selected I for MM9 provided 2 nM, as compared to about 1.5 nM for marimasat. I, and their pharmaceutical compns., are useful for treating asthma, rheumatoid arthritis, COPD, rhinitis, osteoarthritis, psoriatic arthritis, **psoriasis**, pulmonary fibrosis pulmonary inflammation, acute respiratory distress syndrome, periodontosis, multiple sclerosis, gingivitis, atherosclerosis, neointimal proliferation, which leads to restenosis and ischemic heart failure, stroke, renal diseases, tumor metastasis, and other inflammatory disorders characterized by over-expression and over-activation of an matrix metalloproteinase.

L26 ANSWER 4 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN

2006:605026 Document No. 145:46069 Preparation of triazole-substituted aminobenzophenones as inhibitors of the production of IL-1β and TNF-α for the treatment of inflammation, ophthalmic diseases and cancer. Ottosen, Erik Rytter (Leo Pharma A/S, Den.). PCT Int. Appl. WO 2006063585 A1 20060622, 101 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK,

ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-DK757 20051128. PRIORITY: US 2004-635000P 20041213; DK 2004-1942 20041216.

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I and II [wherein R1 = Me, Cl, Br or MeO; R2 = Cl or Me; R3 = (un)substituted alkyl, alkoxy, alkenyl, etc.; R4 - R8 = H, halo, NH2, etc., with exclusions] and pharmaceutically acceptable salts, solvates, or esters thereof were prepared as inhibitors of the production of IL-1β and TNF-α. For instance, III was obtained by cyclization of 2-(2-azidoethoxy)tetrahydropyran with the corresponding phenylacetylene (preparation given) in the presence of copper(II) sulfate pentahydrate and sodium ascorbate. Hydrolysis of this acetal with TsOH in methanol gave a alc., which was found to be highly potent inhibitors of the production of IL-1β and TNF-α with IC50 of 1.3 nM and 0.5 nM, resp., higher than the six reference compds. The alc. was also found to be a potent p38 **MAP kinase** inhibitor (no data). Therefore, the invented compds. are useful, e.g., in the treatment of inflammatory, ophthalmic diseases, or cancer.

L26 ANSWER 5 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
2006:164321 Document No. 144:226281 Method using **MAP kinase** inhibitors and TNF-α **antagonists** for prevention or treatment of inflammatory disease. Firestein, Gary Steven; Boyle, David Louis; Sorkin, Linda Sue (The Regents of the University of California, USA). PCT Int. Appl. WO 2006020365 A2 20060223, 61 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-US26312 20050725. PRIORITY: US 2004-591327P 20040726; US 2004-606580P 20040901.

AB Methods are provided for prevention or treatment of inflammatory disease in a mammal by administering an inhibitor of mitogen-activated (**MAP**) **kinase** system to the mammal in a therapeutic amount to the mammal in need thereof. The **MAP kinase** inhibitor is targeted to the central nervous system of the mammal. Methods are further provided for prevention or treatment of inflammatory disease in a mammal by administering an **antagonist** of TNF-α to the mammal in a therapeutic amount to the mammal in need thereof. The TNF-α **antagonist** is targeted to the central nervous system of the mammal.

L26 ANSWER 6 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
2006:99983 Document No. 144:184708 Use of K-252a and kinase inhibitors for the prevention or treatment of HMGB1-associated pathologies. Fumero, Silvano; Pilato, Francesco, P.; Barone, Domenico; Bertarione, Rava, Rossa, Luisa; Mainero, Valentina; Traversa, Silvio (Creabilis Therapeutics S.p.A., Italy; Bio3research Srl). PCT Int. Appl. WO 2006010628 A1 20060202, 63 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA,

GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-EP8258 20050729. PRIORITY: US 2004-591880P 20040729; US 2005-647007P 20050127.

AB The present invention relates to the use of K-252a, a physiol. active substance produced by microorganisms, and/or a kinase inhibitor and of its salts or synthetic and/or chemical modified derivs. for the prevention or treatment of HMGB1-associated pathologies. More particularly, the present invention relates to the use of K-252a for the prevention or treatment of restenosis.

L26 ANSWER 7 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN

2006:1309587 Document No. 146:55504 Compositions and methods using neurokinin B (NK-B), NK-B analogs, NK receptor agonists and NK receptor **antagonists** for modulating angiogenesis, and their therapeutic use. Bresnick, Emery H.; Paul, Soumen (Wisconsin Alumni Research Foundation (Warf), USA). U.S. Pat. Appl. Publ. US 2006281670 A1 20061214, 56pp. (English). CODEN: USXXCO. APPLICATION: US 2006-450502 20060609. PRIORITY: US 2005-689413P 20050610; US 2005-724104P 20051006.

AB Methods and compns. for modulating angiogenesis are disclosed. Such modulation is made possible by the use of NK-B, NK-B analogs, NK receptor agonists and NK receptor **antagonists** to promote or inhibit angiogenesis. The method for modulating the angiogenic activity of cells comprises contacting cells capable of angiogenesis with an effective amount of NK-B, an NK-B analog, an NK receptor agonist or an NK receptor **antagonist** wherein the angiogenic activity of the cells is increased or decreased. The angiogenesis-modulating compds. can be administered to alleviate and or prevent angiogenesis-related diseases in patients, e.g. cancer, rheumatoid arthritis, macular degeneration, atherosclerosis, coronary artery disease, peripheral vascular disease, varicose veins and preeclampsia.

L26 ANSWER 8 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN

2006:579261 Document No. 145:46068 Preparation of triazole-substituted aminobenzophenones as inhibitors of the production of IL-1β and TNF-α for the treatment of inflammation, ophthalmic diseases and cancer. Erik, Rytter Ottosen (Leo Pharma A/S, Den.). U.S. Pat. Appl. Publ. US 2006128766 A1 20060615, 48 pp. (English). CODEN: USXXCO. APPLICATION: US 2005-292064 20051202. PRIORITY: US 2004-635000P 20041213.

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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I and II [wherein R1 = Me, Cl, Br or MeO; R2 = Cl or Me; R3 = (un)substituted alkyl, alkoxy, alkenyl, etc.; R4 - R8 = H, halo, NH2, etc., with exclusions] and pharmaceutically acceptable salts, solvates, or esters thereof were prepared as inhibitors of the production of IL-1β and TNF-α. For instance, III was obtained by cyclization of 2-(2-azidoethoxy)tetrahydropyran with the corresponding phenylacetylene (preparation given) in the presence of copper(II) sulfate pentahydrate and sodium ascorbate. Hydrolysis of this acetal with TsOH in methanol gave a alc., which was found to be highly potent inhibitors of the production of IL-1β and TNF-α with IC50 of 1.3 nM and 0.5 nM, resp., higher than the six reference compds. The alc. was also found to be a potent p38 **MAP kinase** inhibitor (no data). Therefore, the invented compds. are useful, e.g., in the treatment of inflammatory, ophthalmic diseases, or cancer.

L26 ANSWER 9 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN

2006:490559 Document No. 145:8165 Preparation of octahydropyrrolo[3,4-c]pyrrole derivatives as histamine H4 receptor ligands. Lane, Charlotte Alice Louise; Price, David Anthony (UK). U.S. Pat. Appl. Publ. US 2006111416 A1 20060525, 35 pp. (English). CODEN: USXXCO. APPLICATION:

US 2005-285653 20051121. PRIORITY: EP 2004-106044 20041124; EP 2005-100474 20050126; US 2005-664619P 20050322.

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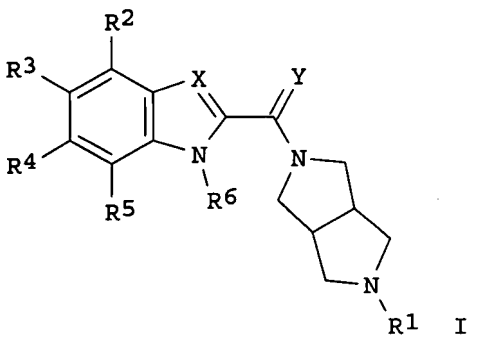
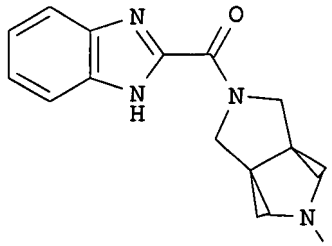


I



II

AB The title compds. I [R1 = H, alkyl optionally substituted with hydroxy; X = N, CR9; Y = O, NH; R2-R5 = H, halo, CN, alkyl, etc.; R6 = H, Me; R9 = H, Me] which are histamine H4 receptor ligands and have therefore a number of therapeutic applications, particularly in the treatment of asthma and allergic rhinitis, were prepared Thus, reacting 1H-benzimidazole-2-carboxylic acid with (3aR,6aS)-2-methyloctahydropyrrolo[3,4-c]pyrrole afforded (3aR,6aS)-II which showed Ki of 91 nM in the H4 binding assay. The pharmaceutical compns. comprising I alone or in combination with other therapeutic agents are disclosed.

L26 ANSWER 10 OF 56 MEDLINE on STN

2006421983. PubMed ID: 16648634. Inhibition of JNK promotes differentiation of epidermal keratinocytes. Gazel Alix; Banno Tomohiro; Walsh Rebecca; Blumenberg Miroslav. (Department of Dermatology, New York University School of Medicine, New York, New York 10016, USA.) The Journal of biological chemistry, (2006 Jul 21) Vol. 281, No. 29, pp. 20530-41. Electronic Publication: 2006-04-28. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB In inflamed tissue, normal signal transduction pathways are altered by extracellular signals. For example, the JNK pathway is activated in psoriatic skin, which makes it an attractive target for treatment. To define comprehensively the JNK-regulated genes in human epidermal keratinocytes, we compared the transcriptional profiles of control and JNK inhibitor-treated keratinocytes, using DNA microarrays. We identified the differentially expressed genes 1, 4, 24, and 48 h after the treatment with SP600125. Surprisingly, the inhibition of JNK in keratinocyte cultures in vitro induces virtually all aspects of epidermal differentiation in vivo: transcription of cornification markers, inhibition of motility, withdrawal from the cell cycle, stratification, and even production of cornified envelopes. The inhibition of JNK also induces the production of enzymes of lipid and steroid metabolism, proteins of the diacylglycerol and inositol phosphate pathways, mitochondrial proteins, histones, and DNA repair enzymes, which have not been associated with differentiation previously. Simultaneously, basal cell markers, including integrins, hemidesmosome and extracellular matrix components, are suppressed. Promoter analysis of regulated genes finds that the binding sites for the forkhead family of transcription factors are over-represented in the SP600125-induced genes and c-Fos sites in the suppressed genes. The JNK-induced proliferation appears to be secondary to inhibition of differentiation. The results indicate that the inhibition of JNK in epidermal keratinocytes is sufficient to initiate their differentiation program and suggest that augmenting JNK activity could be used to delay cornification and enhance wound healing, whereas attenuating it could be a differentiation therapy-based approach for treating **psoriasis.**

L26 ANSWER 11 OF 56 MEDLINE on STN

2006418554. PubMed ID: 16702443. Discovery and characterization of triaminotriazine aniline amides as highly selective p38 kinase inhibitors. Lin Tsung H; Metzger Axel; Diller David J; Desai Madhuri; Henderson Ian; Ahmed Gulzar; Kimble Earl F; Quadros Elizabeth; Webb Maria L. (Pharmacopeia Drug Discovery Inc., P.O. Box 5350, Princeton, NJ 08543-5350, USA.) The Journal of pharmacology and experimental therapeutics, (2006 Aug) Vol. 318, No. 2, pp. 495-502. Electronic Publication: 2006-05-15. Journal code: 0376362. ISSN: 0022-3565. Pub. country: United States. Language: English.

AB The p38 mitogen-activated protein (**MAP**) **kinases** are a family of serine/threonine protein kinases that play important roles in cellular responses to inflammation and external stress. Inhibitors of the p38 **MAP kinase** have shown promise for potential treatment of inflammatory disorders such as rheumatoid arthritis, acute coronary syndrome, **psoriasis**, and Crohn's disease. We identified a novel class of p38 inhibitors via high-throughput screening. PS200981 [3-(4-(1,4-diazepan-1-yl)-6-(((1S,2R,5S)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methylamino)-1,3,5-triazin-2-ylamino)-4-methylbenzamide], a representative compound identified from screening a collection of combinatorial libraries, amounting to 2.1 million compounds, inhibits p38alpha kinase and the lipopolysaccharide (LPS)-induced increase in tumor necrosis factor (TNF) alpha levels in cell media of human monocytes with IC50 values of 1 microM. The screening data revealed a preferred synthon, 3-amino-4-methyl benzamide, which is critical for the activity against p38. This synthon appeared almost exclusively in screening hits including PS200981, and slight variations of this synthon including 3-amino benzamide and 2-amino-4-methyl benzamide also contained in the library were inactive. PS200981 is equally potent against the alpha and beta forms of p38 but did not inhibit p38 gamma and is >25-fold selective versus a panel of other kinases. PS200981 inhibited the LPS-induced increase in TNFalpha levels when administered at 30 mg/kg to mice. Selectivity and in vivo activity of this class of p38 inhibitors was further demonstrated by PS166276 [(R)-3-(4-(isobutyl(methyl)-amino)-6-(pyrrolidin-3-ylamino)-1,3,5-triazin-2-ylamino)-4-methylbenzamide], a highly structurally related but more potent and less cytotoxic inhibitor, in several intracellular signaling assays, and in LPS-challenged mice. Overall, this novel class of p38 inhibitors is potent, active in vitro and in vivo, and is highly selective.

L26 ANSWER 12 OF 56 MEDLINE on STN

2006723819. PubMed ID: 16904202. Calcitonin gene-related peptide regulates the expression of vascular endothelial growth factor in human HaCaT keratinocytes by activation of ERK1/2 MAPK. Yu Xiao-Jing; Li Chun-Yang; Wang Ke-Yu; Dai Hong-Yan. (Department of Dermatology, Qilu Hospital, University of Shandong, Jinan 250-012, China.) Regulatory peptides, (2006 Dec 10) Vol. 137, No. 3, pp. 134-9. Electronic Publication: 2006-08-10. Journal code: 8100479. ISSN: 0167-0115. Pub. country: Netherlands. Language: English.

AB **Psoriasis** is a chronic disease characterized by abnormal epidermal proliferation, inflammation and angiogenesis. The pathogenetic process resulting in hypervascularity remains to be further investigated. It has been reported that a potent angiogenic factor, vascular endothelial growth factor (VEGF) is overexpressed in psoriatic epidermis and that the level of calcitonin gene-related peptide (CGRP) is elevated in **psoriasis** lesions and CGRP-containing neuropeptide nerve fibers are denser in the psoriatic epidermis. We hypothesized that CGRP might regulate the expression of VEGF by human keratinocytes. VEGF expression in the CGRP-treated human keratinocytes was investigated and the CGRP signaling pathways were examined with respect to VEGF expression. The mRNA and protein levels of VEGF by CGRP were increased in a concentration-dependent manner. However, this increase was abrogated by pretreatment with an extracellular signal-regulated kinase (ERK) inhibitor PD98059. The CGRP-mediated VEGF induction was also effectively inhibited by a pretreatment with the CGRP receptor **antagonist** CGRP 8-37.

In addition, CGRP treatment induced rapid phosphorylation of ERK1/2, PD98059 and CGRP 8-37 were able to inhibit CGRP-induced ERK1/2 phosphorylation. These results suggest that CGRP regulates the expression of VEGF through the CGRP receptor and ERK1/2 MAPK signaling pathway in human HaCaT keratinocytes.

L26 ANSWER 13 OF 56 MEDLINE on STN
2006045503. PubMed ID: 16433680. CCL28 production in HaCaT cells was mediated by different signal pathways from CCL27. Kagami Shinji; Saeki Hidehisa; Komine Mayumi; Kakinuma Takashi; Nakamura Koichiro; Tsunemi Yuichiro; Sasaki Kiyo; Asahina Akihiko; Tamaki Kunihiko. (Department of Dermatology, Faculty of Medicine, University of Tokyo, Japan.. kagamis-tky@umin.ac.jp) . Experimental dermatology, (2006 Feb) Vol. 15, No. 2, pp. 95-100. Journal code: 9301549. ISSN: 0906-6705. Pub. country: Denmark. Language: English.
AB Both CCL27 and CCL28 are ligands for CCR10 and attract CCR10(+) lymphocytes. We previously demonstrated that CCL27 and CCL28 were strongly expressed in sera and lesional keratinocytes of patients with atopic dermatitis and **psoriasis** vulgaris. However, the regulation of CCL27 and CCL28 production in keratinocytes has not been well documented. In this study, we showed that CCL27 and CCL28 expression and production by a human keratinocyte cell line, HaCaT cells, were strongly induced by inflammatory cytokines tumor necrosis factor-alpha and interleukin-1beta. CCL27 production was downregulated by inhibitors of p38 mitogen-activated protein kinase and nuclear factor-kappa B (NF-kappaB). By contrast, CCL28 production was downregulated by inhibitors of extracellular signal-regulated kinase and NF-kappaB. Our study results suggest that CCL28 produced by keratinocytes is mediated by different signal pathways from CCL27 and that both CCL27 and CCL28 are involved in the pathogenesis of inflammatory skin diseases.

L26 ANSWER 14 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
2005:99473 Document No. 142:197891 A preparation of nicotinamide derivatives, useful as PDE4 inhibitors. Bailey, Simon; Barber, Christopher Gordon; Glossop, Paul Alan; Middleton, Donald Stuart (Pfizer Limited, UK; Pfizer Inc.). PCT Int. Appl. WO 2005009966 A1 20050203, 210 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-IB2379 20040713. PRIORITY: GB 2003-17516 20030725.
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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to a preparation of nicotinamide derivs. of formula I [wherein: R1 is H, Me, or halogen; R2 is H, OH, alkoxy, or alkyl, etc.; R3 is H or alkyl; R4 is attached to the 3- or 4-position of the Ph ring and is S(O)0-2-alkyl; R5 is H, halogen, alkyl, or alkoxy; X is (CH2)0-1; L is carbocyclic non-aromatic ring], useful as PDE4 inhibitors. For instance, nicotinamide derivative II (TNFα screen: IC50 = 0.4 nM) was prepared via amidation of 2-hydroxy-5-methylbenzoic acid by amine III•HCl with a yield of 39% (example 1).

L26 ANSWER 15 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
2005:99472 Document No. 142:197890 Preparation of nicotinamide derivatives as PDE4 inhibitors. Bunnage, Mark Edward; Mathias, John Paul (Pfizer Limited, UK; Pfizer Inc.). PCT Int. Appl. WO 2005009965 A1 20050203, 102

pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-IB2368 20040713. PRIORITY: GB 2003-17484 20030725.

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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title compds. I [R1, R2 = each independently selected from H, halo, C1-C3 alkyl; R3 = C-linked 5-, or 6-membered heteroaryl containing 1, 2, 3 nitrogen atoms wherein said heteroaryl is substituted by a hydroxy(C1-C4)alkyl group] were prepared as PDE4 inhibitors. For example, reaction of 2-hydroxy-4-hydroxymethylbenzoic acid with syn-N-(4-amino-cyclohexyl)-5-fluoro-2-[3-(methylthio)phenoxy]-nicotinamide hydrochloride yielded compound II. The latter showed an inhibitory activity against PDE4 with IC50 = 0.6 nM.

L26 ANSWER 16 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN

2005:99452 Document No. 142:176548 Preparation of novel aminobenzophenones as inhibitors of interleukin IL-1β and tumor necrosis factor TNF-α production and their use in the treatment of inflammatory diseases and conditions. Ottosen, Erik Rytter; Horneman, Anne Marie; Liang, Xifu; Schou, Soren Christian; Havez, Sophie Elisabeth; Sabroe, Thomas Peter (Leo Pharma A/S, Den.). PCT Int. Appl. WO 2005009940 A1 20050203, 247 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-DK490 20040709. PRIORITY: US 2003-489488P 20030724.

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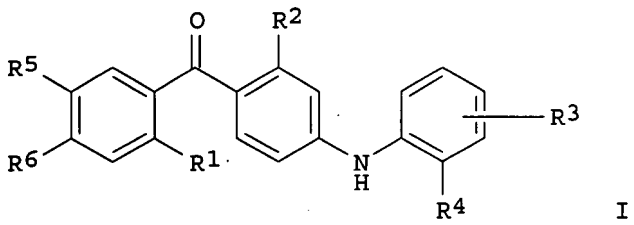

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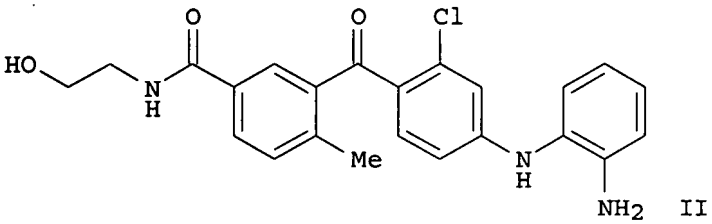

II

AB Title compds. I [wherein R1 = halo, OH, SH, CF3, alk(en/yn)yl, alkoxy, CN, CONH2, NO2, etc.; R2 = H, halo, PH, NO2, CONH2, OH, SH, alk(en/yn)yl, etc.; R3 = one or more, independently H, halo, OH, SH, CN, CO2H, NO2, alkoxycarbonyl, etc.; R4 = H, halo, NO2, etc.; R5, R6 = independently H, CO2H, CONHOH, CONHNH2, (un)substituted alk(en/yn)yl, alkylamino, etc.; with provisos; and their pharmaceutically acceptable salts, solvates and esters] were prepared as inhibitors of interleukin IL-1β and tumor necrosis factor TNF-α production for treating inflammation and related diseases. For example, II was prepared, in 6 steps, from 3-iodo-4-methylbenzoic acid Me ester, 2-chloro-4-nitrobenzoyl chloride, and 1-iodo-2-nitrobenzene. II displayed potent inhibitory activity against p38α **MAP kinase** with IC50 of 2 nM and inhibited production of IL-1β and TNF-α in vitro with IC50 values of 4.0 nM and 0.6 nM. Thus, I are useful in the treatment of inflammatory, ophthalmic diseases or cancer.

L26 ANSWER 17 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN

2005:1004352 Document No. 143:279459 Compositions and methods for preventing and treating skin and hair conditions. David, Nathaniel E. (VVII NewCo 2003, Inc., USA). U.S. Pat. Appl. Publ. US 2005203111 A1 20050915, 16 pp. (English). CODEN: USXXCO. APPLICATION: US 2004-799867 20040312.

AB The present invention discloses compns. and methods for the prevention and treatment of skin and hair diseases, such as, for example, alopecia, **psoriasis**, and keloids. In one embodiment, the present invention discloses a method for preventing and treating hair loss by applying locally to a region lacking hair a p38α **MAP kinase** inhibitor. The p38α **MAP kinase** inhibitor is preferably formulated as a gel, ointment, spray or solution that can be applied topically, transdermally, or s.c. to the targeted region. The p38 inhibitor is especially RDP-58, AMG-548, BIRB-796, CNI-1493, VX-702 or VX-745.

L26 ANSWER 18 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN

2005:99170 Document No. 142:197885 A preparation of nicotinamide derivatives, useful as PDE4 inhibitors. Mathias, John Paul (Pfizer Inc., UK). U.S. Pat. Appl. Publ. US 2005026952 A1 20050203, 27 pp. (English). CODEN: USXXCO. APPLICATION: US 2004-895873 20040720. PRIORITY: GB 2003-17482 20030725; US 2003-497128P 20030822.

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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to a preparation of nicotinamide derivs. of formula I [wherein: R1 and R2 are independently selected from H, halogen, or alkyl; R3 is 9- to 10-membered bicyclic heteroaryl], useful as PDE4 inhibitors. For instance, nicotinamide derivative II (IC50 = 0.07 nM) was prepared via amidation of quinoline-8-sulfonyl chloride by amine III•HCl.

L26 ANSWER 19 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
2005:78241 Document No. 142:176842 Preparation of N-heteroaroylaminocyclohexyl nicotinamides as phosphodiesterase-4 (PDE4) inhibitors. Mathias, John Paul (Pfizer Inc., UK). U.S. Pat. Appl. Publ. US 2005020626 A1 20050127, 28 pp. (English). CODEN: USXXCO. APPLICATION: US 2004-895883 20040720. PRIORITY: GB 2003-17509 20030725; US 2003-497180P 20030822.

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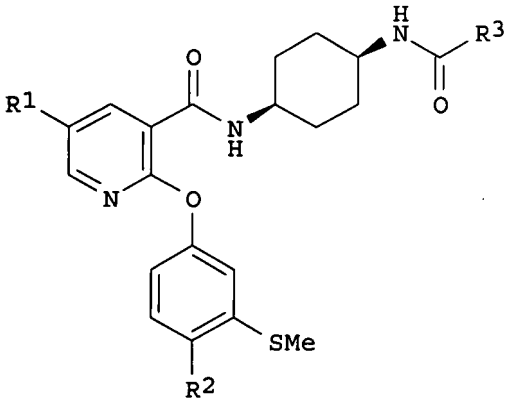

I

AB Title compds. [I; R1, R2 = H, halo, alkyl; R3 = (substituted) 9-10 membered bicyclic heteroaryl containing 1-4 N atoms], were prepared Thus, syn-1H-indazole-3-carboxylic acid [4-[[5-fluoro-2-(3-methylthiophenoxy)pyridine-3-carbonyl]amino]cyclohexyl] amide (preparation outlined) inhibited TNFα release from human peripheral blood mononuclear cells with IC50 = 0.04 nM.

L26 ANSWER 20 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
2005:78237 Document No. 142:176699 A preparation of (thiopyranyloxy)pyridinecarboxamide derivatives, useful as TNF-α and PDE4 inhibitors. Barber, Christopher Gordon; Bunnage, Mark Edward; Harvey, John Wilson; Mathias, John Paul (UK). U.S. Pat. Appl. Publ. US 2005020611 A1 20050127, 52 pp. (English). CODEN: USXXCO. APPLICATION: US 2004-896085 20040720. PRIORITY: GB 2003-17498 20030725; US 2003-497120P 20030822.

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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to a preparation of (thiopyranyloxy)pyridinecarboxamide derivs. of formula I [wherein: R1 is H, halogen, or alkyl; R2 is Ph, Bn, naphthyl, or heteroaryl, etc.; Z is C(O) or SO2], useful as TNF-α and PDE4 inhibitors. For instance, (thiopyranyloxy)pyridinecarboxamide

derivative II (TNF-α inhibition: IC50 = 0.7 nM) was prepared via amidation of 4-hydroxy-2-methoxybenzoic acid by amine III•HCl with a yield of 64%.

L26 ANSWER 21 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
2005:78228 Document No. 142:176698 Preparation of nicotinamide derivatives as PDE4 inhibitors. Bailey, Simon; Barber, Christopher Gordon (Pfizer Inc, USA). U.S. Pat. Appl. Publ. US 2005020587 A1 20050127, 56 pp. (English). CODEN: USXXCO. APPLICATION: US 2004-896355 20040720. PRIORITY: GB 2003-17472 20030725; US 2003-497069P 20030822.
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [X is H, Me, halo; Y is attached to the 3- or 4-position on the Ph ring, and is S(O)pR1; R1 is (un)substituted alkyl by cycloalkyl; p is 0-2; n is 1, 2; Z is H, alkyl, halo, etc.; further details on Y, Z are given; L is 5- or 6- membered heterocyclic ring containing one or two nitrogen ring atoms, which ring is (un)substituted by one to three hydroxy, hydroxyalkyl, alkoxyalkyl, etc.; R2 is (un)substituted alkyl by 5- or 6- membered heterocyclic ring containing one to three hetero atoms, e.g., O, S, said hetero cyclic ring being substituted independently by one to three hydroxy, hydroxyalkyl, alkoxyalkyl, etc.] and their pharmaceutically acceptable salts were prepared For example,N,N'-carbonyldiimidazole mediated acylation of of 5-fluoro-2-(3-methylsulfanylphenoxy)nicotinic acid with 1-(3-aminopyrrolidin-1-yl)ethanone afforded N-(1-acetylpyrrolidin-3-yl)-5-fluoro-2-(3-methylsulfanylphenoxy)nicotinamide (II). In inhibition assays vs. PDE4A, PDE4B and/or PDE4D, the IC50 value of compound II was <3 μM. Compds. I are claimed useful for the treatment of asthma, inflammation, etc.

L26 ANSWER 22 OF 56 MEDLINE on STN
2005028576. PubMed ID: 15654950. Interleukin-6-type cytokines upregulate expression of multidrug resistance-associated proteins in NHEK and dermal fibroblasts. Dreuw Alexandra; Hermanns Heike M; Heise Ruth; Joussen Sylvia; Rodriguez Felipe; Marquardt Yvonne; Jugert Frank; Merk Hans F; Heinrich Peter C; Baron Jens M. (Department of Biochemistry, University Hospital, Aachen, Germany.) The Journal of investigative dermatology, (2005 Jan) Vol. 124, No. 1, pp. 28-37. Journal code: 0426720. ISSN: 0022-202X. Pub. country: United States. Language: English.
AB Normal human epidermal keratinocytes (NHEK) and dermal fibroblasts express a cell-specific pattern of efflux transport proteins. Since regulatory mechanisms for these transporters in cells of the human skin were unknown, we analyzed the influence of inflammatory cytokines on the expression of multidrug resistance-associated proteins (MRP1, 3, 4, 5). Using real-time PCR, RT-PCR, cDNA microarray, immunostaining and efflux assays we demonstrated that stimulation of NHEK and primary human dermal fibroblasts with interleukin-6 (IL-6), in combination with its soluble alpha-receptor, or oncostatin M (OSM) for 24-72 h resulted in an upregulation of MRP expression and activity. Both cytokines induced a strong activation of signal transducer and activator of transcription (STAT)1 and STAT3 as well as the mitogen-activated protein kinase (MAPK) Erk1/2. OSM additionally activated proteinkinase B strongly. Using the MAPK/extracellular signal-regulated kinase kinase 1-specific inhibitor U0126 we could exclude a stimulatory effect of MAPK on MRP gene expression. Inhibition of the phosphatidylinositol 3-kinase, however, indicated that this pathway might be involved of OSM-mediated upregulation of MRP4 in dermal fibroblasts. Several inflammatory skin diseases show an enhanced expression of IL-6-type cytokines. Correspondingly, upregulation of MRP expression was found in lesional skin taken from patients with **psoriasis** and lichen planus.

L26 ANSWER 23 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
2004:1059119 Document No. 142:32932 Combination therapy for cancer and other proliferative disorders. Blatt, Lawrence M.; Seiwert, Scott D.; Ozes, Osman N. (Intermune, Inc., USA). PCT Int. Appl. WO 2004105684 A2 20041209, 635 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US15346 20040513. PRIORITY: US 2003-471841P 20030516; US 2003-485474P 20030708; US 2003-511415P 20031014; US 2003-511280P 20031014; US 2003-511259P 20031014; US 2003-514173P 20031024; US 2004-561940P 20040413.

AB The invention provides methods of treating proliferative disorders, including angiogenesis-mediated disorders, cancer, and fibrotic disorders. In some embodiments, the methods involve administering a Type II interferon receptor agonist and a Type I interferon receptor agonist. In other embodiments, the methods involve administering a Type II interferon receptor agonist, a stress-activated protein kinase (SAPK) inhibitor, and a third therapeutic agent. In other embodiments, the methods involve administering a Type II interferon receptor agonist and a vascular endothelial growth factor (VEGF) **antagonist.** In other embodiments, the methods involve administering a VEGF **antagonist** and a SAPK inhibitor. The invention further provides methods of treating fibrotic disorders. In some embodiments, the methods involve administering a Type I interferon receptor agonist, a Type II interferon receptor agonist; and a tumor necrosis factor (TNF) **antagonist.** In other embodiments, the methods involve administering a Type II interferon receptor agonist and a TNF **antagonist.** In other embodiments, the methods involve administering pirfenidone or a pirfenidone analog and a TNF **antagonist.** In other embodiments, the methods involve administering a Type II interferon receptor agonist and a transforming growth factor-β (TGF-β) **antagonist.** In other embodiments, the methods involve administering a SAPK inhibitor alone or in combination with a Type II interferon receptor agonist. In other embodiments, the methods involve administering N-acetyl cysteine (NAC) and a SAPK inhibitor. In other embodiments, the methods involve administering NAC and a Type II interferon receptor agonist.

L26 ANSWER 24 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
2004:718637 Document No. 141:236649 Methods for identifying and administering agents that bias the immune response via dendritic cells. Pulendran, Bali; Agrawal, Sudhanshu; Dillon, Stephanie Maree (Emory University, USA). PCT Int. Appl. WO 2004074435 A2 20040902, 96 pp. DESIGNATED STATES: W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, ML, MR, NE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US2773 20040130. PRIORITY: US 2003-443692P 20030130; US 2003-516169P 20031031.

AB The invention provides a method of regulating a Th2 immune response which comprises contacting a cell with an amount of a mol. effective to modulate an ERK 1/2 pathway and/or a c-FOS pathway in the cell so as a to regulate the TH2 immune response, which mol. is any of (a) an agonist of a TLR2 (toll-like receptor 2) or a TLR2 variant; (b) an agonist of an intracellular pathway that is initiated by activation of a TLR2; (c) an agonist of an intracellular pathway that is initiated by activation of a

receptor activated by SEA (schistosome egg antigen); (d) an **antagonist** of an intracellular pathway that opposes TLR2 signaling or activation; (e) an agonist of an ERK 1/2 pathway; (f) an **antagonist** of a p38 pathway; (g) an **antagonist** of a JNK 1/2 pathway; or (h) an agonist of the c-FOS pathway, or a mol. that induces c-Fos gene expression, c-Fos mRNA stability, c-Fos protein induction, c-Fos protein stability, or c-Fos protein phosphorylation.

L26 ANSWER 25 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
2004:467984 Document No. 141:22217 Therapy of non-malignant diseases or disorders with anti-ErbB2 antibodies. Sliwkowski, Mark X.; Brunetta, Paul G. (Genentech, Inc., USA). PCT Int. Appl. WO 2004048525 A2 20040610, 74 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US37367 20031121. PRIORITY: US 2002-428027P 20021121.

AB The authors disclose the preparation and biol. activity of murine and humanized antibodies to HER2. In one example, an anti-HER2 antibody is shown to inhibit heregulin-induced activation of Akt kinase and erbB2 association with erbB3. The present application describes treatment of non-malignant indications, such as **psoriasis**, endometriosis, scleroderma, vascular diseases or disorders, respiratory disease, colon polyps or fibroadenoma, with anti-ErbB2 antibodies (e.g. rhuMAb 2C4).

L26 ANSWER 26 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
2004:430863 Document No. 141:12274 Carboxylic acid derivatives inhibition of the binding of integrins to their receptors. Vanderslice, Peter; Holland, George; Shih, Neng-Yang; Aslanian, Robert G.; Chapman, Richard W.; Kreutner, William (Encysive Pharmaceuticals, USA; Schering Corporation). PCT Int. Appl. WO 2004044046 A2 20040527, 52 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US35526 20031107. PRIORITY: US 2002-424928P 20021108.

AB A composition, method and kit comprise a compound for the inhibition of the binding of $\alpha 4\beta 1$ integrin to its receptors, e.g., VCAM-1 and fibronectin and other therapeutic compds. for the control or prevention of diseases states in which $\alpha 4\beta 1$ is involved.

L26 ANSWER 27 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
2004:142968 Document No. 140:193056 Combinations of active agents with p38 **MAP kinase** inhibitors, pharmaceutical compositions, and use in the treatment of cytokine-mediated diseases. Simianer, Stefan; Bilbault, Pascal; Cappola, Michael L.; Way, Susan Lynn (Boehringer Ingelheim Pharmaceuticals, Inc., USA; Boehringer Ingelheim France). PCT Int. Appl. WO 2004014387 A1 20040219, 168 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US25341 20030812. PRIORITY: US 2002-403115P 20020813.

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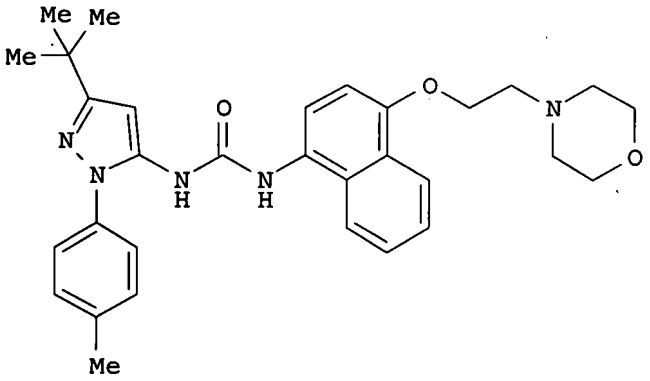

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AB The invention relates to pharmaceutical combination therapies based on p38 kinase inhibitors and another active ingredients, pharmaceutical compns. comprising such combinations, processes for preparing them, and their use in the treatment of cytokine-mediated diseases. Preparation of I (BIRB 796 BS) is described.

L26 ANSWER 28 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
2004:293395 Document No. 140:303676 Preparation of hydantoins as inhibitors of matrix metalloproteinases and/or TNF-α converting enzyme (TACE). Sheppeck, James (Bristol-Myers Squibb Company, USA). U.S. Pat. Appl. Publ. US 2004067996 A1 20040408, 43 pp. (English). CODEN: USXXCO. APPLICATION: US 2003-677988 20031002. PRIORITY: US 2002-416349P 20021004.

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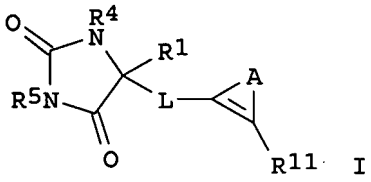

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AB Title compds. [I; R1 = Q, alkylene-Q, alkenylene-Q, alkynylene-Q, (CRaRa1)tO(CRaRa1)s-Q, (CRaRa1)tNRa(CRaRa1)s-Q, (CRaRa1)rCO(CRaRa1)s-Q, (CRaRa1)rCO2(CRaRa1)s-Q, (CRaRa1)tO2C(CRaRa1)s-Q, (CRaRa1)rCONRaRa1, (CRaRa1)rCONRa(CRaRa1)s-Q, (CRaRa1)tNRaCO(CRaRa1)s-Q, (CRaRa1)tOCO2(CRaRa1)s-Q, (CRaRa1)tO2CNRa(CRaRa1)s-Q, (CRaRa1)tNRaCO2(CRaRa1)s-Q, (CRaRa1)tNRaCONRa(CRaRa1)s-Q, (CRaRa1)tS(CRaRa1)s-Q, (CRaRa1)tSO(CRaRa 1)s-Q, (CRaRa1)rSO2(CRaRa1)-Q, (CRaRa1)SO2NRa(CRaRa1)s-Q, (CRaRa1)tNRaSO2(CRaRa1)s-Q, (CRaRa1)tNRaSO2NRa(CRaRa1)s-Q; L = bond, CO, CR2R3; R2 = Q1, alkylene-Q1, etc.; R3 = Q, alkylene-Q, etc.; R4, R5 = H, alkyl, alkenyl, alkynyl; R11 = WUXYZUaXaYaZa; A = atoms to form a 5-6 membered (fused) aryl, heteroaryl; Q = H, CHF2, CH2F, CF3, (substituted) carbocyclyl, heterocyclyl; Q1 = H, (substituted) carbocyclyl, heterocyclyl; Ra = H, alkyl, Ph, PhCH2; Ra1 = H, (substituted) alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl; W = (CRaRa1)m, alkylene, alkynylene; U, Ua = O, NRa1, CO, etc.; X, Xa = null, alkylene, alkenylene, alkynylene; Y, Ya = null, O, NRa1, S, SO, SO2, CO; Z, Za = (substituted) carbocyclyl, heterocyclyl; m = 0-3; r, s = 0-4; t = 1-4], were prepared Thus, 2-aminobenzyl alc and 4-[(2-methyl-4-quinolinyl)methoxy]benzoyl chloride were stirred 20 h in CH2Cl2/aqueous NaHCO3 to give 88% amide, which was stirred with Dess-Martin periodinane in

CH2Cl2/DMF to give 100% aldehyde. The latter was heated with (NH4)2CO3 and KCN in EtOH/H2O at 80° for 24 h to give 10% N-[2-(2,5-dioxoimidazolidin-4-yl)phenyl]-4-[(2-methylquinolin-4-yl)methoxy]benzamide trifluoroacetate. Selected I inhibited matrix metalloproteinases with IC50 ≤10 μM.

L26 ANSWER 29 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN

2004:658040 Discovery and progression of a novel series of orally active p38 kinase inhibitors. Leftheris, Katerina; Ahmed, Gulzar; Chan, Ray; Dyckman, Alaric; Hynes, John; Lin, Shuqun; Metzger, Axel; Moriarty, Kevin; Shimshock, Yvonne; Wen, James; Wityak, John; Wrobleski, Stephen; Wu, Hong; Wu, Junjun; Behnia, Kamelia; Doweyko, Arthur M.; Gillooly, Kathleen; Lin, Tsung; Loo, Derek; McIntyre, Kim; Pitt, Sidney; Shen, Ding Ren; Shuster, David; Zhang, Hongjian; Zhang, Rosemary; Barrish, Joel; Dodd, John; Henderson, Ian; Schieven, Gary; Webb, Maria (Discovery Chemistry, Pharmaceutical Research Institute, Bristol-Myers Squibb, Princeton, NJ, 08543-4000, USA). Abstracts of Papers, 228th ACS National Meeting, Philadelphia, PA, United States, August 22-26, 2004, MEDI-176. American Chemical Society: Washington, D. C. (English) 2004. CODEN: 69FTZ8.

AB Overprodn. of cytokines such as TNF-α and IL-1β are implicated in a wide variety of inflammatory diseases, including rheumatoid arthritis (RA), **psoriasis**, inflammatory bowel disease and endotoxic shock, among others. There is convincing clin. evidence that protein **antagonists** of cytokines such as the soluble TNF-α receptor Fc fusion protein (etanercept), anti-TNF antibody (infliximab) and the IL-1 receptor **antagonist** (anakinra) can effectively treat chronic inflammatory diseases. The stress-activated signal transduction pathway leading to inflammatory cytokine production in stimulated immune cells is known to be regulated in part by p38α mitogen activated protein (**MAP**) **kinase.** To this end, we and others have searched for inhibitors of p38α as a means to inhibit inflammatory cytokine production Herein, we describe our initial efforts in developing potent, selective triaminotriazine amides as inhibitors of p38α **MAP kinase.** Our initial hit was identified through screening the Pharmacopeia compound collection. The lead compound possesses oral activity in in vivo models of acute and chronic inflammatory disease and represents a unique structural class compared to known p38 inhibitors. X-ray crystallog. demonstrates that this compound accesses the ATP binding pocket of p38α, forming a key hydrogen bond through a water mol. A description of SAR progression, in vivo activity, profiling and X-ray crystallog. will be discussed.

L26 ANSWER 30 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN

2003:991488 Document No. 140:27834 Preparation of pyridazinyloximes as phosphodiesterase IV inhibitors.. Eggenweiler, Hans-Michael; Beier, Norbert; Schelling, Pierre; Wolf, Michael (Merck Patent G.m.b.H., Germany). PCT Int. Appl. WO 2003104205 A1 20031218, 137 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (German). CODEN: PIXXD2. APPLICATION: WO 2003-EP5173 20030516. PRIORITY: DE 2002-10225574 20020610.

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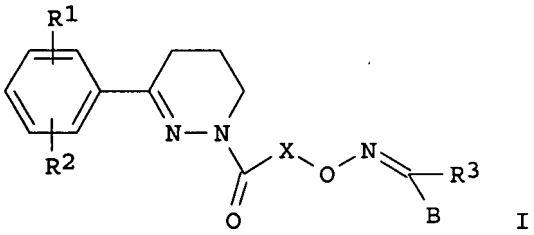

I

AB Title compds. [I; R1, R2 = H, OH, OR8, SR8, SOR8, SO2R8, halo; R1R2 = OCH2O, OCH2CH2O; R3 = H, AR7, COAR7, CO2AR7, CONH2, NH2, etc.; R7 = H, CO2H, NH2, OH, etc.; R8 = (substituted) alkyl, alkenyl, cycloalkyl, alkylenecycloalkyl, etc.; A = null, (O, S, SO, SO2, imino-interrupted) alkylene, alkenylene, cycloalkylene; B = (substituted) aryl, heteroaryl; X = (O, S, SO, SO2, imino-interrupted) alkylene], were prepared as phosphodiesterase IV inhibitors for treating osteoporosis, tumors, cachexia, atherosclerosis, rheumatoid arthritis, multiple sclerosis, diabetes mellitus, inflammatory processes, allergies, asthma, autoimmune diseases, myocardial diseases and AIDS (no data). Thus, 3-(3-ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazine was treated sequentially with chloroacetyl chloride, N-hydroxyphthalimide, ethanolamine, and 4-methoxybenzaldehyde to give 4-methoxybenzaldehyde O-[2-[3-(3-ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-2-oxoethyl]oxime.

L26 ANSWER 31 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN

2003:777532 Document No. 139:296920 Uracil derivatives as inhibitors of TNF-α converting enzyme (TACE) and matrix metalloproteinases. Maduskuie, Thomas P. (Bristol-Myers Squibb Company, USA). PCT Int. Appl. WO 2003079986 A2 20031002, 105 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US8412 20030314. PRIORITY: US 2002-365334P 20020318.

AB The present application describes novel uracil derivs. of formula I: A-W-U-X-Y-Z-Ua-Xa-Ya-Za or pharmaceutically acceptable salt or prodrug forms thereof, wherein A, W, U, X, Y, Z, Ua, Xa, Ya, and Za are defined in the present specification, which are useful as inhibitors of TNF-α converting enzyme (TACE), matrix metalloproteinases (MMP), aggrecanase or a combination thereof.

L26 ANSWER 32 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN

2003:511307 Document No. 139:85368 Preparation of barbituric acids as inhibitors of TNF-α converting enzyme (TACE), aggrecanase and/or matrix metalloproteinases. Duan, Jingwu; Jiang, Bin; Chen, Lihua; Lu, Zhonghui; Barbosa, Joseph; Pitts, William (Bristol-Myers Squibb Company, USA). PCT Int. Appl. WO 2003053941 A2 20030703, 267 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US40458 20021217. PRIORITY: US 2001-342658P 20011220.

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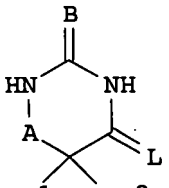

R^1 $CR^2R^3(CR^4R^5)_nWUXYZU?X?Y?Z?$ I

AB The present application describes novel barbituric acid derivs. (shown as I; variables defined below; e.g. 5-methyl-5-[3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-3-oxopropyl]-2,4,6(1H,3H,5H)-pyrimidinetrione) or pharmaceutically acceptable salt or prodrug forms thereof, which are useful as TNF-α converting enzyme (TACE), aggrecanase and matrix metalloproteinases (MMP) inhibitors. Although the methods of preparation are not claimed, 60 example prepns. are included. Some examples of I (specific compds. not stated) inhibit matrix metalloproteinases with Ki ≤10 μM. For I: A is C(O), C(S) or CH2; B is O or S; L is O or S; W = (CRaRa1)m, C2-3 alkenylene, and C2-3 alkynylene; U = C(O), CRa(OH), C(O)O, OC(O), C(O)NRa1, NRa1C(O), OC(O)O, OC(O)NRa1, NRa1C(O)O, and NRa1C(O)NRa1; X is absent or C1-3 alkylene, C2-3 alkenylene, and C2-3 alkynylene; Y is absent or O, NRa1, S(O)p, and C(O); Z = C3-13 carbocycle substituted with 0-5 Rb, and a 5-14 membered heterocycle comprising C atoms and 1-4 heteroatoms N, O, and S(O)p, and substituted with 0-5 Rb; Ua is absent or O, NRa1, C(O), CRa(OH), C(O)O, OC(O), C(O)NRa1, NRa1C(O), OC(O)O, OC(O)NRa1, NRa1C(O)O, NRa1C(O)NRa1, S(O)p, S(O)pNRa1, NRa1S(O)p, and NRa1SO2NRa1; Xa is absent or C1-10-alkylene, C2-10 alkenylene, and C2-10 alkynylene; Ya is absent or O, NRa1, S(O)p, and C(O); Za = C3-13 carbocycle substituted with 0-5 Rc and a 5-14 membered heterocycle comprising C atoms and 1-4 heteroatoms N, O, and S(O)p, and substituted with 0-5 Rc. R1 = CHF2, CH2F, CF3, C1-6 alkylene-Q (Q = H, CF3, etc.), etc.; R2 = Q1 (Q1 = H, carbocyclyl, heterocyclyl), C1-6 alkylene-Q1, etc.; R3 = Q, C1-6 alkylene-Q, etc.; R4, R5 = H, C1-6 alkyl, etc.; addnl. details including provisos are given in the claims.

L26 ANSWER 33 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
2003:511306 Document No. 139:85367 Preparation of barbituric acids as inhibitors of TNF-α converting enzyme (TACE), aggrecanase and/or matrix metalloproteinases. Duan, Jingwu; Lu, Zhonghui (Bristol-Myers Squibb Company, USA). PCT Int. Appl. WO 2003053940 A1 20030703, 123 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US40202 20021217. PRIORITY: US 2001-342649P 20011220.

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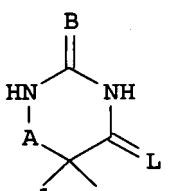

R^1 $WZU?X?Y?Z?$ I

AB The present application describes novel barbituric acid derivs. (shown as I; variables defined below; e.g. 5-Methyl-5-[4-[(2-methyl-4-quinolinyl)methoxy]benzyl]-2,4,6(1H,3H,5H)-pyrimidinetrione trifluoroacetate) or pharmaceutically acceptable salt or prodrug forms thereof, which are useful as TNF-α converting enzyme (TACE), aggrecanase and matrix metalloproteinases (MMP) inhibitors. Although the methods of preparation are not claimed, 37 example prepns. are included. Some examples of I (specific compds. not stated) inhibit matrix metalloproteinases with Ki ≤10 μM. For I: A is C(O), C(S) or CH2; B is O or S; L is O or S; W = (CRaRa1)m, C2-3 alkenylene, and C2-3 alkynylene; Z = C6-10 aryl substituted with 0-5 Rb and a 5-14 membered heteroaryl comprising C atoms and 1-4 heteroatoms N, O, and S(O)p, and substituted with 0-5 Rb; Ua is absent or O, NRa1, C(O), CRa(OH), C(O)O, OC(O), C(O)NRa1, NRa1C(O), OC(O)O, OC(O)NRa1, NRa1C(O)O, NRa1C(O)NRa1, S(O)p, S(O)pNRa1, NRa1S(O)p, and NRa1SO2NRa1; Xa is absent or C1-10 alkylene, C2-10 alkenylene, and C2-10 alkynylene; Ya is absent or O, NRa1, S(O)p, and C(O); Za = C3-13 carbocycle substituted with 0-5 Rc and a 5-14 membered heterocycle comprising C atoms and 1-4 heteroatoms N, O, and S(O)p, and substituted with 0-5 Rc. R1 = CHF2, CH2F, CF3, C1-6 alkylene-Q (Q = H, CHF2, CH2F, CF3, C3-13 carbocyclyl, etc.), etc.; addnl. details including provisos are given in the claims.

L26 ANSWER 34 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN

2003:376826 Document No. 138:385302 Heterocyclic β-sulfone derivatives of hydroxamic acids as inhibitors of matrix metalloproteinases and/or TNF-α converting enzyme (TACE) for treating inflammatory disorders. Duan, Jingwu; Ott, Gregory (Bristol-Myers Squibb Company, USA). PCT Int. Appl. WO 2003040103 A1 20030515, 198 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US35327 20021101. PRIORITY: US 2001-335962P 20011102.

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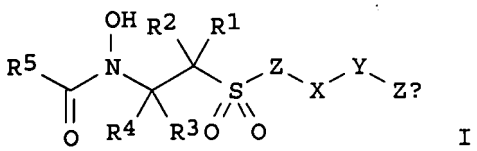

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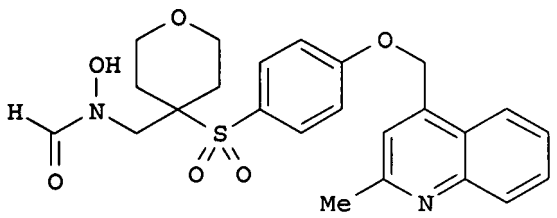

II

AB Title compds. I [wherein R1 and R4 = independently H or (un)substituted alkyl, alkenyl, or alkynyl; R2 = Q, alkylene-Q, alkenylene-Q,

alkynylene-Q, etc.; R3 = Q1, alkylene-Q1, alkenylene-Q1, alkynylene-Q1, etc.; Q and Q1 = independently H or (un)substituted (hetero)cyclyl; or CR3R4 = (un)substituted (hetero)cyclyl; R5 = H or alkyl; XY = CH2, CH2O, or OCH2; Z = (un)substituted (hetero)aryl; Za = (un)substituted 8-14 membered heterocyclyl containing 1-3 N atoms and 0-1 O, S, SO, and/or SO2; and pharmaceutically acceptable salt or prodrugs thereof] are useful as inhibitors of matrix metalloproteinases (MMP), TNF-α converting enzyme (TACE), aggrecanase, or a combination thereof. Preps. for several compds. of the invention are given (no data), and six specific compds. are claimed. For example, a 9-step synthesis for the [[(quinolinylmethoxy)phenyl]sulfonyl]-substituted N-hydroxy-N-(tetrahydropyranylmethyl)formamide II is given. A number of I exhibited Ki values of <10 μM in MMP assays (specific compds. not mentioned). Thus, I are useful for the treatment of conditions or diseases mediated by MMPs, TACE, or aggrecanase, such as inflammatory disorders (no data).

L26 ANSWER 35 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN

2003:376641 Document No. 138:385438 Preparation of pyridazinylmethanoylphenylhydrazonomalonitriles as phosphodiesterase IV inhibitors.. Eggenweiler, Hans-Michael; Wolf, Michael; Beier, Norbert; Schelling, Pierre; Ehring, Thomas (Merck Patent Gmbh, Germany). PCT Int. Appl. WO 2003039548 A1 20030515, 114 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-EP11351 20021010. PRIORITY: EP 2001-125455 20011105.

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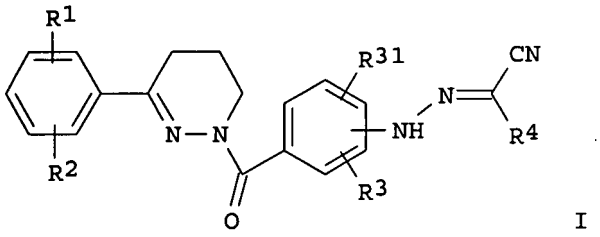

I

AB Title compds. [I; R1, R2 = H, OH, OR5, SR5, SOR5, SO2R5, X; R1R2 = OCH2O, OCH2CH2O; R3, R31 = H, R5, OH, OR5, NH2, NHR5, NHCOR5, X, CO2H, CO2R5, CONH2, etc.; R4 = cyano, tetrazolyl; R5 = (fluoro-substituted) A, cycloalkyl, (CH2)nAr; A = (fluoro- and/or chloro-substituted) alkyl, alkenyl; Ar = Ph; n = 0-2; X = F, Cl, Br, iodo], were prepared Thus, [3-(3,4-diethoxyphenyl)-5,6-dihydro-4H-pyridazine-1-yl]-(3-aminophenyl)methanone (preparation given) was stirred with NaNO2 in aqueous HCl for 1 h at -2° to 0°; malononitrile in H2O was added followed by stirring for 2 h to give a residue which was treated with KOH in MeOH to give 2-[[3-[1-[3-(3,4-diethoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]methanoyl]phenyl]hydrazono]malononitrile K salt. I were said to give a marked reduction of T cell proliferation. I are claimed for treatment of osteoporosis, tumors, cachexia, atherosclerosis, rheumatoid arthritis, multiple sclerosis, diabetes mellitus, inflammatory processes, allergies, asthma, autoimmune diseases, myocardial diseases, AIDS, etc.

L26 ANSWER 36 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN

2003:356269 Document No. 138:348761 Type 4 phosphodiesterase inhibitors and therapeutic uses thereof. Eggenweiler, Hans-Michael; Wolf, Michael (Merck

Patent G.m.b.H., Germany). PCT Int. Appl. WO 2003037349 A1 20030508, 122 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-EP9596 20020828. PRIORITY: EP 2001-125394 20011031.

AB The invention discloses the use of type 4 phosphodiesterase inhibitors (PDE IV inhibitors) to treat diseases, as well as combinations of PDE IV inhibitors with other drugs.

L26 ANSWER 37 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN

2003:301073 Document No. 138:321300 Preparation of cyclic sulfone derivatives as inhibitors of matrix metalloproteinases, aggrecanase and/or TNF-α converting enzyme (TACE). Duan, Jingwu; Xue, Chu-Biao (Bristol-Myers Squibb Company, USA). PCT Int. Appl. WO 2003031431 A1 20030417, 115 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US32168 20021007. PRIORITY: US 2001-327816P 20011009.

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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present formula application describes novel cyclic sulfone derivs. (shown as I; variables defined below; e.g. N-hydroxy-2-[4-isopropyl-2-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-1,1-dioxido-2-thiomorpholinyl]acetamide (shown as II)) or pharmaceutically acceptable salt or prodrug forms thereof, which are useful as inhibitors of matrix metalloproteinases (MMP), TNF-α converting enzyme (TACE), aggrecanase, or a combination thereof. Although the methods of preparation are not claimed, 1 example preparation is included and 19 specific I are mentioned in the claims. For I: A = COR5, CO2H, CO2R6, C(O)NHOH, C(O)NHOR5, C(O)NHOR6, NHRa, N(OH)COR5, N(OH)CHO, SH, CH2SH, S(O)(:NH)Ra, S(:NH)2Ra, SC(O)Ra, PO(OH)2, and PO(OH)NHRa. Ring B, including the shown C and sulfonyl groups, is a 4-8 membered heterocycle consisting of C atoms and, in addition to the sulfonyl group shown, 0-2 heteroatoms = O, N, NR10, and S(O)p, provided that ring B contains other than a S-S, O-O, or S-O bond; ring B consists of 0-1 double bonds and is substituted with 0-2 Rb. X is absent or is CR3R4; Ua is absent or = O, NRa1, C(O), C(O)O, OC(O), C(O)NRa1, NRa1C(O), OC(O)O, OC(O)NRa1, NRa1C(O)O, NRa1C(O)NRa1, S(O)p, S(O)pNRa1, NRa1S(O)p, and NRa1SO2NRa1; Xa is absent or = C1-4 alkylene, C2-4 alkenylene, and C2-4 alkynylene; Ya is absent or = O, NRa1, S(O)p, and C(O); provided that Ua-Xa-Ya form other than a bond or O; Za is a C3-13 carbocycle substituted with 0-5 Rc or a 5-14 membered heterocycle consisting of C atoms and 1-4 heteroatoms N, O, and S(O)p, and substituted with 0-5 Rc; provided that Ua, Ya and Za do not combine to form a N-N, N-O, O-N, O-O, S(O)p-O, O-S(O)p or S(O)p-S(O)p group. R1 = H, C1-6 alkyl substituted with 0-1 Rb, C2-6 alkenyl substituted with 0-1 Rb, and C2-6 alkynyl substituted with 0-1 Rb; R2 = Q, C1-6 alkylene-Q, C2-6 alkenylene-Q, C2-6 alkynylene-Q, (CRaRa1)r10(CRaRa1)r-Q, (CRaRa1)r1NRa(CRaRa1)r-Q, (CRaRa1)r1C(O)(CRaRa1)r-Q, (CRaRa1)r1C(O)O(CRaRa1)r-Q, (CRaRa1)r1OC(O)(CRaRa1)r-Q, (CRaRa1)r1C(O)NRaRa1, (CRaRa1)r1C(O)NRa(CRaRa1)r-Q,

(CRaRa1)r1NRaC(O)(CRaRa1)r-Q, (CRaRa1)r1OC(O)O(CRaRa1)r-Q, (CRaRa1)r1OC(O)NRa(CRaRa1)r-Q (CRaRa1)r1NRaC(O)O(CRaRa1)r-Q, (CRaRa1)r1NRaC(O)NRa(CRaRa1)r-Q, (CRaRa1)r1S(O)p(CRaRa1)r-Q, (CRaRa1)r1SO2NRa(CRaRa1)r-Q, (CRaRa1)r1NRaSO2(CRaRa1)r-Q, and (CRaRa1)r1NRaSO2NRa(CRaRa1)r-Q; Q = H, a C3-13 carbocycle substituted with 0-5 Rd, and a 5-14 membered heterocycle consisting of C atoms and 1-4 heteroatoms N, O, and S(O)p, and substituted with 0-5 Rd; alternatively, R1 and R2, together with the C atom to which they are attached, combine to form a 3-10 membered heterocyclic ring consisting of C atoms and 0-2 ring heteroatoms = O, N, NR10, and S(O)p, and substituted with 0-3 Rc;. Rb = C1-6 alkyl substituted with 0-1 Rc1, ORa, Cl, F, Br, I, O, CN, NO2, NRaRa1, C(O)Ra, C (O)ORa, C(O)NRaRa1, C(S)NRaRa1, NRaC(O)NRaRa1, OC(O)NRaRa1, NRaC(O)ORa, S(O)2NRaRa1, NRaS(O)2Ra3, NRaS(O)2NRaRa1, OS(O)2NRaRa1, NRaS(O)2Ra3, S(O)pRa3, CF3, CF2CF3, CHF2, CH2F, and phenyl; q = 0-2; addnl. details are given in the claims. A number of I exhibit Ki's of <10 μM in a metalloproteinase assay (specific compds. not mentioned).

L26 ANSWER 38 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN

2003:242278 Document No. 138:271682 Preparation of cyclic hydroxamic acids as inhibitors of matrix metalloproteinases and/or TNF-α converting enzyme for treatment of inflammatory disorders. Ott, Gregory; Chen, Xiao-Tao; Duan, Jingwu; Lu, Zhonghui (Bristol-Myers Squibb Company, USA). PCT Int. Appl. WO 2003024899 A2 20030327, 344 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US29685 20020916. PRIORITY: US 2001-322630P 20010917.

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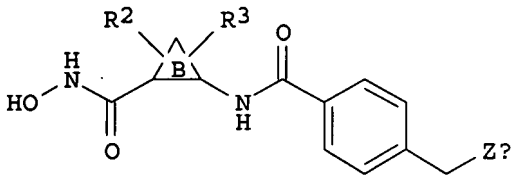

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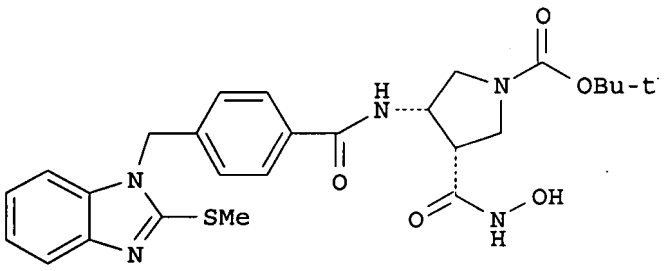

II

AB Title compds. I [wherein ring B = (un)substituted 4-7 membered (hetero)cyclic ring containing 0-2 O, N, NR1, or SOp atoms and 0-3 carbonyl groups; R1 and R2 = independently Q, alk(en/yn)ylene-Q, or (un)substituted alkylene-Q interrupted by O, NRa, CO, CO2, CONRa, NRaCO, NRaCO2, NRaCONRa, SOp, NRaSO2, or SO2NRa; or R1 = (un)substituted alkylene-Q interrupted by OCO, OCO2, or OCONRa; Q = H or (un)substituted (hetero)cyclyl; R3 = Q1,

Cl, F, alk(en/yn)ylene-Q1, or (un)substituted alkylene-Q1 interrupted by O, NR1, NRaCO, CONRa, CO, CO2, SOp, or SO2NRa; Q1 = H or (un)substituted Ph, naphthyl, or heterocyclyl; Za = (un)substituted benzimidazolyl, indolyl, imidazopyridinyl, pyrazolylpyridinyl, benzofuranyl, benzothiazinyl, quinolinyl, etc.; Ra = independently H, alkyl, Ph, or benzyl; p = 0-2; or stereoisomers or pharmaceutically acceptable salts thereof] were prepared as inhibitors of matrix metalloproteinases (MMP), TNF-a converting enzyme (TACE), aggrecanase, or a combination thereof. For example, reaction of benzyl Me maleate with paraformaldehyde and glycine gave benzyl Me (cis)-3,4-pyrrolidinedicarboxlyate (100%). BOC-protection (64%), debenzylation (96%), resolution of the (3S,4S)-isomer with (S)-α-methylbenzylamine, conversion to the carbamate with DPPA and PhCH2OH (76%), and Pd catalyzed hydrogenation (100%) provided Me (3S,4S)-4-amino-1-(tert-butoxycarbonyl)-3-pyrrolidinecarboxylate. Coupling of the amine with 4-[(2-methylthio-1H-benzimidazol-1-yl)methyl]benzoic acid (preparation given) afforded the amide (99%), which was treated with NH2OH•HCl/MeONa to give the hydroxamic acid (3S,4S)-II (33%). A number of the compds. of the invention inhibited MMP-1, 2, 3, 7, 8, 9, 10, 12, 13, 14, 15, and/or 16 with Ki values of ≤ 10 μM. Thus, I are useful for the treatment of a wide variety of inflammatory disorders (no data).

L26 ANSWER 39 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN

2003:154378 Document No. 138:205082 Preparation of bicyclic hydroxamates as inhibitors of matrix metalloproteinases and/or TNF-α converting enzyme (TACE) for treating inflammatory disorders. Sheppeck, James; Duan, Jingwu (Bristol-Myers Squibb Company Patent Department, USA). PCT Int. Appl. WO 2003016248 A2 20030227, 102 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US26018 20020815. PRIORITY: US 2001-313052P 20010817.

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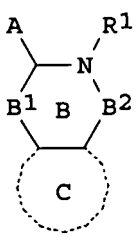

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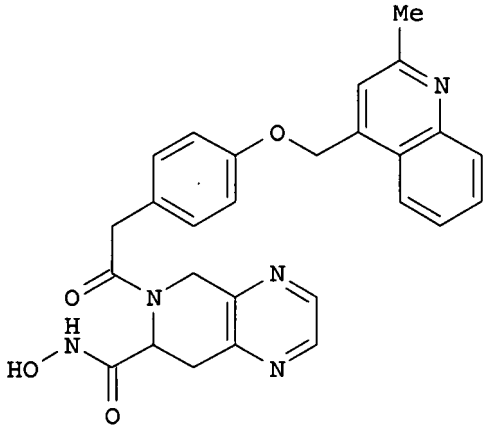


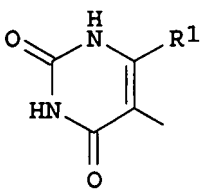
II

AB The title compds. [I; A = CONHOH, CONHOR5, CONHOR6, N(OH)COR5, N(OH)CHO, CH2SH; ring B, including B1 and B2, = (un)substituted 5-7 membered heterocyclic ring; B1, B2 consist of 0-3 carbon atoms and 0-1 heteroatoms selected from O, N, and SOp and are substituted with 0-1 carbonyl groups; ring C = (un)substituted 5-10 membered aromatic ring consisting of 1-9 carbon

atoms and 0-4 heteroatoms selected from O, N, and SOp; R1 = {4-[(2-methyl-4-quinolinyl)methoxy]phenyl}acetyl, {4-[(2-methyl-4-quinolinyl)methoxy]phenyl}sulfonyl, etc.; R5 = (un)substituted alkyl; R6 = Ph, naphthyl, cycloalkyl, etc.], useful as inhibitors of matrix metalloproteinases (MMP), TNF-α converting enzyme (TACE), aggrecanase, or a combination thereof, were prepared and formulated. E.g., a 5-step synthesis of II as bis-TFA salt, starting from 2,3-dimethylpyrazine, was given. A number of compds. I were found to exhibit Ki's of ≤10 μM in MMP assays.

L26 ANSWER 40 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
2003:971727 Document No. 140:16741 Preparation of uracil derivatives as inhibitors of TNF-α converting enzyme (TACE) and matrix metalloproteinases. Maduskuie, Thomas P. (Bristol-Myers Squibb Company, USA). U.S. Pat. Appl. Publ. US 2003229081 A1 20031211, 31 pp. (English). CODEN: USXXCO. APPLICATION: US 2003-389529 20030314. PRIORITY: US 2002-365334P 20020318.

GI



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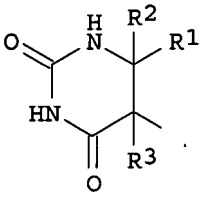

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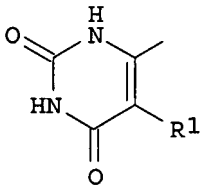

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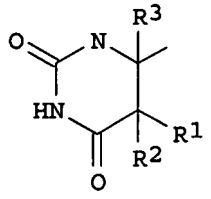
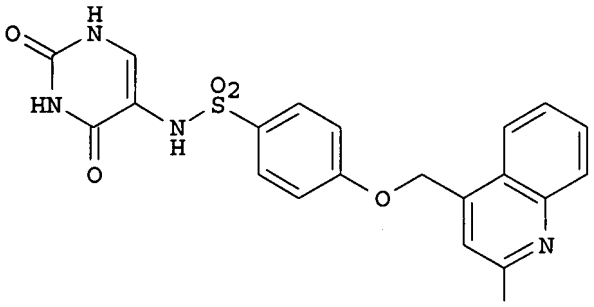


V



VI

AB The title compds. A-W-U-X-Y-Z-Ua-Xa-Ya-Za [I; A = II-V; W = a bond, O, CO, CO2, (un)substituted NH, etc.; X = a bond, alkylene, alkenylene, alkynylene; Y = a bond, O, (un)substituted NH, SOp, CO; Z = carbocycle, heterocycle; Ua = O, CO, OCO, CO2, etc.; Xa = a bond, alkylene, alkenylene, alkynylene; Ya = a bond, O, CO, SOp, (un)substituted NH; Za = H, carbocyle, heterocycle; provided that U, Y, Z, Ua, Ya, and Za do not combine to form NN, NO, ON, OO, SOpO, OSOp, SOpSOp group; R1 = H, CF3, alkyl, etc.; R2 = H, alkyl, alkenyl, alkynyl; R3 = H, alkyl, alkenyl, alkynyl; p = 0-2; with the provisos], useful as inhibitors of TNF-α converting enzyme (TACE), matrix metalloproteinases (MMP), aggrecanase or a combination thereof, were prepared E.g., a 3-step synthesis of VI.TFA (starting from 4-hydroxybenzenesulfonic acid sodium salt and 4-chloromethyl-2-methylquinoline), was given. A number of compds. I were found to exhibit Ki's of ≤ 10 μM in MMP assays. The pharmaceutical composition comprising the compound I is claimed.

L26 ANSWER 41 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
2003:506580 Document No. 139:79178 Synthesis of 3H-pyrrolo[2,3-d]pyrimidine

derivatives and use as phosphodiesterase VII inhibitors and in combination with other agents. Eggenweiler, Hans-Michael; Wolf, Michael (Merck Patent GmbH, Germany). Ger. Offen. DE 10163991 A1 20030703, 36 pp. (German). CODEN: GWXXBX. APPLICATION: DE 2001-10163991 20011224.

AB The invention concerns the synthesis of 3H-pyrrolo[2,3-d]pyrimidine derivs., their physiol. acceptable salts, stereoisomers, solvates, mixts. thereof and their use as phosphodiesterase VII inhibitors in the treatment of diseases that are influenced by the phosphodiesterase VII regulation of human eosinophil activation and degranulation. Osteoporesis, tumors, cachexia, atherosclerosis, rheumatoid arthritis, multiple sclerosis, diabetes mellitus, AIDS, autoimmune and heart diseases can be treated with the drugs. Thus the synthesis of 5-isopropyl-4-oxo-7-p-tolyl-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid Et ester and analog compds. is described along with injection, suppository, tablet and other formulations.

L26 ANSWER 42 OF 56 MEDLINE on STN

2003388705. PubMed ID: 12925217. Histamine enhances the production of nerve growth factor in human keratinocytes. Kanda Naoko; Watanabe Shinichi. (Department of Dermatology, Teikyo University, School of Medicine, 11-1 Kaga-2, Itabashi-Ku, Tokyo 173-8605, Japan.. nmk@med.teikyo-u.ac.jp) . The Journal of investigative dermatology, (2003 Sep) Vol. 121, No. 3, pp. 570-7. Journal code: 0426720. ISSN: 0022-202X. Pub. country: United States. Language: English.

AB Nerve growth factor induces innervation and epidermal hyperplasia in inflammatory skin diseases like **psoriasis.** Nerve growth factor production by keratinocytes is increased in the inflammatory lesions. Nerve growth factor induces histamine release from mast cells. We examined the in vitro effects of histamine on nerve growth factor production in human keratinocytes. Histamine enhanced nerve growth factor secretion, mRNA expression, and promoter activity in keratinocytes. Two TPA-response elements on the nerve growth factor promoter were responsible for the activation by histamine. Histamine enhanced transcriptional activity and DNA binding of activator protein 1 at the two TPA-response elements. It shifted the TPA-response-element-binding activator protein 1 composition from c-Jun homodimers to c-Fos/c-Jun heterodimers. Histamine transiently induced c-Fos mRNA expression, which was not detectable in unstimulated keratinocytes, whereas c-Jun mRNA expression was constitutive and was not altered by histamine. Histamine-induced enhancement of nerve growth factor secretion, promoter activity, activator protein 1 transcriptional activity, and c-Fos expression was suppressed by H1 **antagonist** pyrilamine, protein kinase C inhibitor calphostin C, and PD98059, an inhibitor of mitogen-activated protein kinase kinase 1. Histamine induced the translocation of protein kinase C activity from cytosol to membrane, which was suppressed by phospholipase C inhibitor U73122. It stimulated the phosphorylation of extracellular signal-regulated kinase, which was blocked by pyrilamine, calphostin C, and PD98059. These results suggest that histamine may enhance nerve growth factor production by inducing c-Fos expression in keratinocytes. These effects may be mediated by the H1-receptor-induced signaling cascade of phospholipase C-protein kinase C-mitogen-activated protein kinase kinase 1-extracellular signal-regulated kinase.

L26 ANSWER 43 OF 56 MEDLINE on STN

2003028613. PubMed ID: 12535196. Bone morphogenetic proteins and their **antagonists** in skin and hair follicle biology. Botchkarev Vladimir A. (Department of Dermatology, Boston University School of Medicine, Boston, MA 02118, USA.. VLadbotc@bu.edu) . The Journal of investigative dermatology, (2003 Jan) Vol. 120, No. 1, pp. 36-47. Ref: 176. Journal code: 0426720. ISSN: 0022-202X. Pub. country: United States. Language: English.

AB Bone morphogenetic proteins (BMP) are members of the transforming growth factor-beta superfamily regulating a large variety of biologic responses in many different cells and tissues during embryonic development and postnatal life. BMP exert their biologic effects via binding to two types

of serine/threonine kinase BMP receptors, activation of which leads to phosphorylation and translocation into the nucleus of intracellular signaling molecules, including Smad1, Smad5, and Smad8 ("canonical" BMP signaling pathway). BMP effects are also mediated by activation of the mitogen-activated protein (**MAP**) **kinase** pathway ("noncanonical" BMP Signaling pathway). BMP activity is regulated by diffusible BMP **antagonists** that prevent BMP interactions with BMP receptors thus modulating BMP effects in tissues. During skin development, BMPs its receptors and **antagonists** show stringent spatiotemporal expressions patterns to achieve proper regulation of cell proliferation and differentiation in the epidermis and in the hair follicle. In normal postnatal skin, BMP are involved in the control of epidermal homeostasis, hair follicle growth, and melanogenesis. Furthermore, BMP are implicated in a variety of pathobiologic processes in skin, including wound healing, **psoriasis**, and carcinogenesis. Therefore, BMPs represent new important players in the molecular network regulating homeostasis in normal and diseased skin. Pharmacologic modulation of BMP signaling may be used as a new approach for managing skin and hair disorders.

L26 ANSWER 44 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN

2002:927249 Document No. 138:14059 Preparation of spiro-fused hydantoin derivatives as inhibitors of matrix metalloproteinases. Sheppeck, James E.; Duan, Jingwu; Xue, Chu-Biao; Wasserman, Zelda (Bristol-Myers Squibb Company, USA). PCT Int. Appl. WO 2002096426 A1 20021205, 350 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US16381 20020523. PRIORITY: US 2001-293571P 20010525.

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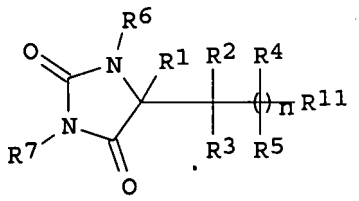

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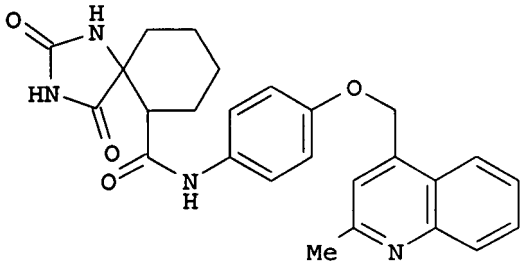

II

AB Title compds. I [R11 = W-U-X-Y-Z-Ua-Xa-Ya-Za; W = alkyl, alkenylene, alkynylene; U = absent, amino, CO, alkyl, carboxy, etc.; X = absent,

alk(en/yn)ylene; Y = absent, O, amino, SO0-2, CO; Z = (hetero)cycle; Ua = absent, O, amino, CO, alkyl, carboxy, etc.; Xa = absent, alk(en/yn)ylene; Ya = absent, O, amino, SO0-2, CO; Za = (hetero)cycle; R1-2 together with the carbon atoms to which they are attached, combine to form a 3-8 membered carbocyclic or heterocyclic ring; R3 = H, CHF2, CH2F, CF3, alk(en/yn)ylene, etc.; R4-7 = H, alk(en/yn)yl; n = 0-1] were prepared For instance, 2-(ethylcarboxy)cyclohexanone was treated with ammonium carbonate and potassium cyanide (EtOHaq, 50°, 24 h) to afford the corresponding hydantoin ester which was hydrolyzed to the carboxylic acid and coupled to 4-[(2-methyl-4-quinolinyl)methoxy]aniline•2HCl (DMSO, PyBOP) to give II which was isolated as the trifluoroacetate. I are useful as inhibitors of matrix metallproteinases (MMP), TNF-α converting enzyme (TACE), aggrecanase, or a combination thereof.

L26 ANSWER 45 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN

2002:814087 Document No. 137:325234 Preparation of aminophenyl (hetero)aryl ketones as p38 **MAP kinase** inhibitors for treatment of inflammatory diseases or conditions. Havez, Sophie Elisabeth (Leo Pharma A/S, Den.). PCT Int. Appl. WO 2002083622 A2 20021024, 69 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-DK236 20020410. PRIORITY: US 2001-282494P 20010410.

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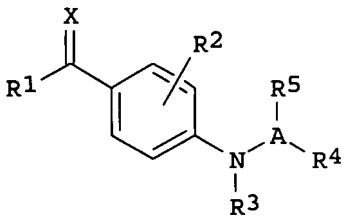

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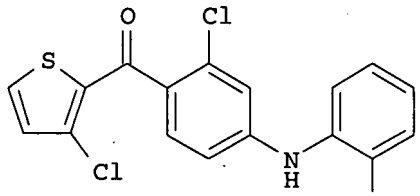

II

AB Title compds. I [wherein R1 = (un)substituted heteroaryl; X = O, S, N(OH), or NR8; R8 = H or alkyl; R2 = H, halo(alkyl), hydroxy(alkyl), SH, CN, NO2, (cyclo)alkyl, alkenyl, alkynyl, aralkyl, alkylaryl, (ar)alkoxy, alkylthio, alkoxycarbonyl, alkylcarbonylamino, alkylcarboxy, alkylcarbonyl, NR6R7, or CONR6R7; R3 = H, (cyclo)alkyl, (cyclo)alkenyl, alkynyl, CO2H, or aryl; A = (hetero)aryl; R4 = H, halo(alkyl), hydroxy(alkyl), SH, CN, CO2H, NO2, (cyclo)alkyl, (cyclo)alkenyl, alkynyl, heterocycloalkyl, (hetero)aryl, aralkyl, alkylaryl, (ar)alkoxy, alkylthio, alkoxycarbonyl, alkylcarbonylamino, aminocarboaminoalkyl, aminosulfonyl, alkylsulfonylamino, alkylcarboxy, alkoxycarboxy, alkylsulfonyloxy, alkoxysulfonyl, alkylcarbonyl, NR6R7, or CONR6R7; R5 = H, halo(alkyl), hydroxy(alkyl), SH, CN, CO2H, carbamoyl, NH2, NO2, (cyclo)alkyl, (cyclo)alkenyl, alkynyl, heterocycloalkyl, (hetero)aryl, aralkyl, alkylaryl, (ar)alkoxy, alkylthio, alkoxycarbonyl, alkylcarbonylamino, aminocarboaminoalkyl, aminosulfonyl, alkylsulfonylamino, alkylcarboxy, alkoxycarboxy, alkylsulfonyloxy, alkoxysulfonyl, alkylcarbonyl, NR6R7, or CONR6R7; R6 and R7 = independently H, alkyl, aryl, etc.; or pharmaceutically acceptable salts, hydrates, solvates, or esters thereof] were prepared as inhibitors of **MAP kinases**, in particular the p38 **MAP kinase**. For example, 2-bromo-3-chlorothiophene was coupled with 2-chloro-4-nitrobenzoyl chloride to give 2-chloro-4-nitrophenyl 3-chloro-2-thienyl ketone (44%), which was reduced to the amine (95%). Addition of 2-bromotoluene afforded II

(31%). The latter displayed potent inhibitory activity against p38α **MAP kinase** with IC50 of 93.3 nM and inhibited production of IL-1β, TNF-α, and PMN-superoxide with IC50 values of 72 nM, 17 nM, and 6.3 nM, resp. Thus, I and compns. of I with other active components are useful as antiinflammatory agents in the prophylaxis or treatment of inflammatory diseases or conditions (no data).

L26 ANSWER 46 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
2002:594822 Document No. 137:154857 Preparation of nicotinamide biaryl derivatives as inhibitors of PDE4 isozymes. Chambers, Robert James; Magee, Thomas Victor; Marfat, Anthony (Pfizer Products Inc., USA). PCT Int. Appl. WO 2002060875 A1 20020808, 224 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-IB2341 20011206. PRIORITY: US 2001-265492P 20010131.
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title compds. [I; g = 0-1; j = 0-1; provided that when j = 0, n must be 2; k = 0-1; m = 0-2; n = 1-2; W1 = 0, SOt (t = 0-2), NR3; W2 = OCR9R10, or absent; Y = CR1, NOk (k = 0-1); R9, R10 = H, F, CF3, etc.; or R9 and R10 are taken together, but only in the case where m = 1, to form a spiro moiety; R7, R8 have the same meaning as R9, R10 except that one of them must be H; R1, R2 = H, F, Cl, etc.; R3 = H, alkyl, Ph, etc.; R4-R6 = H, F, Cl, etc.; Q1 = Ph, benzodioxyl, etc.; Q2 = biaryl moiety], useful as inhibitors of PDE4 in the treatment of diseases regulated by the activation and degranulation of eosinophils, especially asthma, chronic bronchitis, and chronic obstructive pulmonary disease, were prepared E.g., a multi-step synthesis of the amide II, starting from Me 3-bromobenzoate and 4-formylbenzeneboronic acid, was given. Compds. I showed anti-inflammatory activity at 0.0001 μM to 20.0 μM in whole blood assay for LTE4.

L26 ANSWER 47 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
2002:814743 Document No. 137:336734 Cloning and characterization of human interleukin-1ε. Sims, John E.; Smith, Dirk E. (Immunex Corporation, USA). U.S. Pat. Appl. Publ. US 2002155506 A1 20021024, 35 pp., Cont.-in-part of U.S. Ser. No. 763,498. (English). CODEN: USXXCO. APPLICATION: US 2001-970033 20011002. PRIORITY: US 1998-97413P 19980821; US 1998-98595P 19980831; US 1998-99974P 19980911; WO 1999-US18771 19990820; US 2001-763498 20010515; US 2001-313110P 20010816.
AB The authors disclose the cloning and sequence characterization of human interleukin-1ε (IL-1ε). In addition, the authors disclose signaling components of the IL-1ε pathway, inducers of IL-1ε, and tissue expression for IL-1ε in health and disease.

L26 ANSWER 48 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
2002:591707 Document No. 137:140509 Preparation of nicotinamides and mimetics as inhibitors of phosphodiesterase IV isozymes. Chambers, Robert J.; Magee, Thomas V.; Marfat, Anthony (Pfizer Products Inc., USA). Eur. Pat. Appl. EP 1229034 A1 20020807, 180 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR. (English). CODEN: EPXXDW. APPLICATION: EP 2002-250202 20020111. PRIORITY: US 2001-265240P 20010131.
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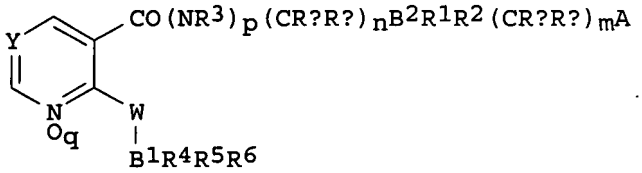

I

AB Title compds. [I; p, q = 0, 1; m = 0-2; n = 1, 2; A = CO2R7, CONR9CO2R7, CONR7R9, OP(O)(OH)2, SO3H, acylsulfonamido, etc.; W = O, S, SO, SO2, NR3; Y = N, NO, CR11; R1, R2 = H, F, Cl, cyano, NO2, alkyl, alkynyl, fluoroalkyl, etc.; R3 = H, alkyl, Ph, PhCH2, etc.; R4-R6 = H, F, Cl, alkynyl, cyano, NO2, etc.; R7 = H, (substituted) alkyl, alkenyl, alkynyl; R9 = H, alkyl, cycloalkyl, Ph, PhCH2, pyridyl, etc.; R11 = H, F, Cl, cyano, NO2, alkyl, alkynyl, fluoroalkyl, fluoroalkoxy, etc.; Ra, Rb = H, F, CF3, alkyl, (substituted) cycloalkyl, Ph, PhCH2; B1, B2 = 3-7 membered (hetero)cyclyl, 7-12 membered poly(hetero)cyclyl; pairs of variables may form rings; with provisos], were prepared (no data). Thus, Me 2-[4-[[[2-(benzo[1,3]dioxol-5-yloxy)pyridine-3-carbonyl]amino]methyl]phenyl]-2-methylpropionate was suspended in Me3COH. Aqueous NaOH was added to the suspension, and the reaction mixture was refluxed 1 h to give 2-[4-[[[2-(benzo[1,3]dioxol-5-yloxy)pyridine-3-carbonyl]amino]methyl]phenyl]-2-methylpropionic acid.

L26 ANSWER 49 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN

2001:747784 Document No. 135:303878 Preparation of 5-(4-pyridyl)thiazoles as p38MAP kinase inhibitors and inhibitors of TNF-α production. Ohkawa, Shigenori; Naruo, Ken-ichi; Miwatashi, Seiji; Kimura, Hiroyuki (Takeda Chemical Industries, Ltd., Japan). PCT Int. Appl. WO 2001074811 A2 20011011, 288 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-JP2629 20010329. PRIORITY: JP 2000-97876 20000330; JP 2001-27571 20010202.

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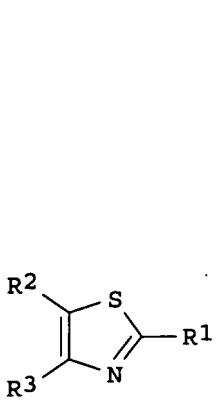

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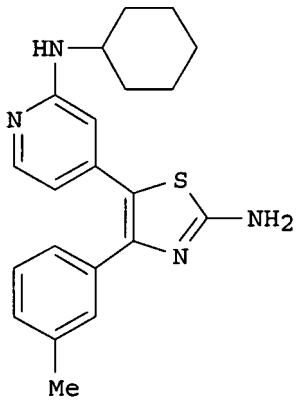

II

AB Title compds. I [wherein R1 = H or (un)substituted hydrocarbon, heterocycle, amino, or acyl; R2 = non-aryl substituted 4-pyridyl; R3 = (un)substituted aryl; or salt thereof] were prepared and showed excellent

p38MAP kinase inhibitory activity. For example, [5-(2-fluoro-4-pyridyl)-4-(3-methylphenyl)-1,3-thiazol-2-yl]amine was stirred with cyclohexylamine at 150°C for 3 h to give II. The latter inhibited p38MAP kinase and TNF-α with IC50 values of 0.0099 μM and 0.002 μM, resp. I are useful for the treatment of a broad variety of cytokine-mediated and adenosine receptor-mediated diseases (no data).

L26 ANSWER 50 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN

2001:380399 Document No. 134:361399 Use of thiazole derivatives for treatment/prevention of p38 kinase-mediated disorders. Ingelman-Sundberg, Magnus; Simi, Anastasia; Tindberg, Niclas (Astrazeneca AB, Swed.). PCT Int. Appl. WO 2001035959 A1 20010525, 26 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-SE2252 20001115. PRIORITY: SE 1999-4177 19991118.

AB The present invention relates to the thiazole derivs., geometrical and optical isomers, tautomers and racemates thereof where such isomers or tautomers exist, as well as pharmaceutically acceptable acid addition salts thereof and solvates thereof, for the preparation of a medicament for the treatment and/or prevention of p38 **MAP kinase**-mediated disorders, such as inflammation, neurol. disorders, hepatic diseases, arthritis, cachexia, autoimmune diseases, endotoxic shock, ophthalmic diseases, etc. The thiazole compds. have been evaluated biol. (1) in rat cortical glial cultures, (2) in human neuroblastoma cell lines, and (3) in in vitro immunocomplex kinase assays. The results showed that the imidazole derivative 4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)1H-imidazole (SB 203580), but not 5-(2-chloroethyl)-4-methylthiazole (clomethiazole) or 1-(4-methyl-5-thiazolyl)-1-phenylmethylamine, inhibited p38 **MAP kinase** in this assay. The results demonstrate that the thiazole compds. of the invention and imidazole derivs. such as SB 203580 act by different mechanisms when interfering with p38 **MAP kinase** pathways.

L26 ANSWER 51 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN

2001:320109 Document No. 134:339545 Processed human chemokines PHC-1 and PHC-2, their sequences, ability to bind CCR receptors, recombinant production, and therapeutic and diagnostic uses. Forssmann, Wolf-Georg; Detheux, Michel; Parmentier, Marc; Staendker, Ludger (Euroscreen S.A., Belg.; Kirchhoff, Frank). PCT Int. Appl. WO 2001031016 A2 20010503, 50 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-BE128 20001025. PRIORITY: DE 1999-19951336 19991025; EP 2000-870140 20000622.

AB The invention provides processed human chemokines designated PHC-1 and PHC-2, or biol. active fragments thereof, which can be modified by or linked to amide, acetyl, phosphoryl and/or glycosyl groups. The invention relates that human chemokine PHC-2 is a fragment of PHC-1, and that both chemokines bind to receptors selected from the group consisting of CCR-1, CCR-3 and CCR-5 receptors. The invention also provides polynucleotide mols. encoding chemokines PHC-1 and PHC-2, vectors containing said polynucleotide mols., and cells transformed with said vectors. The invention further provides **antagonists** (inhibitors) of said chemokines PHC-1 and PHC-2, and/or polynucleotides encoding them, which

include antibodies, antisense oligonucleotides and/or ribozymes. Still further the invention provides: (1) methods for identifying compds. that act as agonists and/or **antagonists** of said chemokines PHC-1 and PHC-2; (2) pharmaceutical composition comprising said chemokines PHC-1 and PHC-2, polynucleotides encoding them, or identified **antagonist** of said chemokines; (3) use of said pharmaceutical composition in the manufacture of medicament which can be used in prevention and/or treatment of diseases induced by viral infections and/or immune-related diseases. Finally, the invention provides the amino acid sequence of the human chemokines PHC-1 and PHC-2. The invention also included the amino acid sequence of chemokine HCC-1, and suggests that PHC-1 and PHC-2 are most likely the naturally processed and highly biol. active forms of HCC-1 chemokine. The invention demonstrated that PHC-1 binding to different chemokine receptors (including CCR1, CCR3 and CCR5) and affected the chemotaxis/migration of immune cells. The invention also demonstrated PHC-1 inhibited HIV-1 entry and replication in human cells, and identified the protease that cleaved the HCC-1 into PHC-1.

L26 ANSWER 52 OF 56 MEDLINE on STN
2002046958. PubMed ID: 11774793. p38 **MAP kinase**: molecular target for the inhibition of pro-inflammatory cytokines. Adams J L; Badger A M; Kumar S; Lee J C. (Smith Kline Beecham Pharmaceuticals, 709 Swedeland Road, King of Prussia, PA 19406, USA.) Progress in medicinal chemistry, (2001) Vol. 38, pp. 1-60. Ref: 286. Journal code: 0376452. ISSN: 0079-6468. Pub. country: Netherlands. Language: English.

L26 ANSWER 53 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
2000:772628 Document No. 133:321879 Preparation of 5-pyridyl-1,3-azole compounds as **antagonists** of adenosine A3 receptor, process for producing the same and use thereof. Ohkawa, Shigenori; Kanzaki, Naoyuki; Miwatashi, Seiji (Takeda Chemical Industries, Ltd., Japan). PCT Int. Appl. WO 2000064894 A1 20001102, 152 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MA, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2000-JP2575 20000420. PRIORITY: JP 1999-116686 19990423; JP 1999-224650 19990806.

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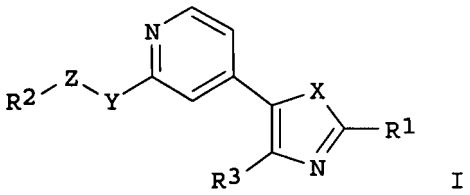

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AB Optionally N-oxidized compds. represented by general formula (I) salts thereof [wherein R1 represents hydrogen, hydrocarbyl, a heterocycle, amino or acyl; R2 represents an aromatic group; R3 represents hydrogen, pyridyl or aromatic hydrocarbyl; X represents oxygen or optionally oxidized sulfur; Y represents a bond, oxygen, optionally oxidized sulfur or NR4 (wherein R4 represents hydrogen, hydrocarbyl, or acyl); and Z represents a bond or a divalent chain hydrocarbyl] are prepared These compds. are usable as preventives or remedies for diseases in association with adenosine A3 receptor because of having excellent adenosine A3 receptor antagonism thereof.

Moreover, the compds. I or salts thereof exhibit excellent effects of inhibiting p38 **MAP kinase** and inhibiting TNF-α and, therefore, are also usable as preventives or remedies for diseases in association with p38 **MAP kinase** or TNF-α. Above diseases include asthma, allergies, brain edema, cerebral vascular disorders, head injuries, inflammation, Addison's disease, autoimmune hemolytic anemia, Crohn's disease, **psoriasis**, rheumatism, spinal cord injury, multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, diabetes, arthritis, septicemia, ulcerative colitis, chronic pneumonia, silicosis, lung sarcoidosis, pulmonary tuberculosis, cachexia, arteriosclerosis, Creutzfeldt-Jakob disease, virus infection, atopic dermatitis, systemic lupus erythematosus, AIDS encephalopathy, meningitis, angina pectoris, myocardial infarction, ischemic heart failure, hepatitis, transplant, dialysis hypotension, and frequent disseminated intravascular coagulation. Thus, bromination of 2-(2-benzoylamino-4-pyridyl)-1-(4-methoxyphenyl)ethanone with Br in AcOH at room temperature for 1 h followed by cyclocondensation of the bromination product with thiourea in the presence of Et3N in MeCN at 80° for 5 h gave N-[4-[2-amino-4-(4-methoxyphenyl)-1,3-thiazol-5-yl]-2-pyridyl]benzamide (II). II showed IC50 of 0.020 μM against p38 **MAP kinase** and 0.014 μM for inhibiting the production of TNF-α in THP-1 cells.

L26 ANSWER 54 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN

2000:688272 Document No. 133:280563 Human antibodies that bind human IL-12 and methods for producing. Salfeld, Jochen G.; Roguska, Michael; Paskind, Michael; Banerjee, Subhashis; Tracey, Daniel E.; White, Michael; Kaymakcalan, Zehra; Labkovsky, Boris; Sakorafas, Paul; Friedrich, Stuart; Myles, Angela; Veldman, Geertruida M.; Venturini, Amy; Warne, Nicholas W.; Widom, Angela; Elvin, John G.; Duncan, Alexander R.; Derbyshire, Elaine J.; Carmen, Sara; Smith, Stephen; Holtet, Thor Las; Du, Fou Sarah L. (Basf A.-G., Germany; Genetics Institute Inc.; et al.). PCT Int. Appl. WO 2000056772 A1 20000928, 377 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US7946 20000324. PRIORITY: US 1999-PV126603 19990325.

AB Human antibodies, preferably recombinant human antibodies, that specifically bind to human interleukin-12 (hIL-12) are disclosed. Preferred antibodies have high affinity for hIL-12 and neutralize hIL-12 activity in vitro and in vivo . An antibody of the invention can be a full-length antibody or an antigen-binding portion thereof. The antibodies, or antibody portions, of the invention are useful for detecting hIL-12 and for inhibiting hIL-12 activity, e.g., in a human subject suffering from a disorder in which hIL-12 activity is detrimental. Nucleic acids, vectors and host cells for expressing the recombinant human antibodies of the invention, and methods of synthesizing the recombinant human antibodies, are also encompassed by the invention.

L26 ANSWER 55 OF 56 MEDLINE on STN

2000294600. PubMed ID: 10836611. TNF-alpha and serum induce SKALP/elafin gene expression in human keratinocytes by a p38 **MAP kinase**-dependent pathway. Pfundt R; Wingens M; Bergers M; Zweers M; Frenken M; Schalkwijk J. (Department of Dermatology, University Hospital Nijmegen, The Netherlands.) Archives of dermatological research, (2000 Apr) Vol. 292, No. 4, pp. 180-7. Journal code: 8000462. ISSN: 0340-3696. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Keratinocytes of inflamed epidermis (**psoriasis**, wound healing) are hyperproliferative and display an abnormal differentiation programme.

This regenerative differentiation pathway is characterized by the induction of genes that are not expressed by keratinocytes in normal skin, such as the cytokeratins CK6, CK16, CK17, and the proteinase inhibitor SKALP/elafin. In the study reported here we investigated the induction and regulation of SKALP expression as a marker for regenerative differentiation in epidermal keratinocytes. Various cytokines and growth factors known to be present in psoriatic epidermis were examined for their ability to induce SKALP gene expression in cultured human keratinocytes. Tumour necrosis factor-alpha (TNF-alpha) and serum were found to be potent inducers of SKALP expression at both the mRNA and the protein levels. SB202190 or SB203580, two specific p38 **MAP kinase** inhibitors almost completely blocked the induction of SKALP expression by TNF-alpha and serum. These results suggest that in keratinocytes, p38 activity is crucial for the induction of SKALP gene expression. These findings could be relevant for the elucidation of the mechanisms involved in normal and disturbed epidermal differentiation.

L26 ANSWER 56 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
1999:393031 Document No. 131:40587 Cloning and expression of CSAID binding protein CSBPβ cDNA and its potential use in drug screening and genetic diagnosis. McDonnel, Peter Colon; Young, Peter Ronald (SmithKline Beecham Corporation, USA). Eur. Pat. Appl. EP 922762 A1 19990616, 27 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI. (English). CODEN: EPXXDW. APPLICATION: EP 1997-309793 19971204.

AB This invention provides protein and cDNA sequences for a newly identified human protein, designated cytokine suppressive anti-inflammatory drug (CSAID) binding protein CSBPβ, which is believed to be a member of the **MAP kinase** family of serine-threonine kinases. CSBPβ is structurally related to other proteins of the CSBP family with the nucleotide sequence of this invention having about 58-73% homol. with other human members of the **MAP kinase** family. A Northern blot conducted with a partial cDNA revealed that CSBPβ was expressed most abundantly in human testis, with lower expression in pancreas, prostate, and small intestine. CSBPβ is useful directly as a therapeutic or diagnostic agent as well as a component in a screening system for compds. which are **antagonists** or agonists of CSAID binding activity.

=> s ErbB antagonist
L27 9 ERBB ANTAGONIST

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PROCESSING COMPLETED FOR L27
L28 6 DUP REMOVE L27 (3 DUPLICATES REMOVED)

=> d l28 1-6 cbib abs

L28 ANSWER 1 OF 6 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
2006:496515 Document No.: PREV200600502835. Age-related rise in colorectal adenomas is associated with increased EGF-receptor expression. Misra, Sudha Reddy Sabeena; Jaszewski, Richard; Xu, Hu; Levi, Edi; Ullah, Nadeem; Majumdar, Adhip P. N.. Gastroenterology, (APR 2006) Vol. 130, No. 4, Suppl. 2, pp. A147.
Meeting Info.: Digestive Disease Week Meeting/107th Annual Meeting of the American-Gastroenterological-Association. Los Angeles, CA, USA. May 19 -24, 2006. Amer Gastroenterol Assoc Inst.
CODEN: GASTAB. ISSN: 0016-5085. Language: English.

AB Although the incidence of colorectal and other gastrointestinal cancers increases with advancing age, reason for this increase is poorly understood. Earlier studies from this and other laboratories have demonstrated that at least in Fischer-344 rats, aging is associated with increased proliferative activity and decreased apoptosis in the colonic mucosa (Mech. Ageing Dev. 122: 1849-1864, 2001). Morphological studies

of the colonic mucosa of human volunteers have also revealed that cell proliferation in the young is confined to the lower two-thirds of the crypt, while with aging there is a major shift from the base to the middle and upper-third of the gland, a pattern that is commonly seen in colorectal cancer. Although the regulatory mechanisms for the age-related rise in mucosal proliferation and reduction in apoptosis have not been fully delineated, we have reported that these events are associated with increased expression and activation of EGF-Receptor (EGER) and reduction in EGF-Receptor Related Protein (ERRP), a negative regulator of EGER (Dig. Dis. Sci. 48: 856-864, 2003). An inverse relationship of EGER and ERRP has been observed in colorectal cancer (Cancer Lett. 213: 249-255, 2004). To determine whether aging predisposes the colon to the processes of carcinogenesis, we examined the relationship between aging and formation of colonic adenomas, the most frequent premalignant colorectal lesion. In our study there were 177 patients with colorectal adenomas in different age groups. Our data show that the number of polyps formed increase with advancing age (age in years: 1 polyps in < 51 yrs; 2 polyps in 51-60; 3 polyps in 61-70 yrs; 4 polyps in 71-80; 5 polys in 80 yrs = 0.95). The age-related rise in polyp formation was associated with a concomitant increase in EGER expression in the macroscopically normal rectal mucosa. The levels of phosphorylated (active) form of EGFR was also higher in macroscopically normal rectal mucosa from 60-70 years old patients with colonic adenomas, when compared with their younger counterparts. On the other hand, levels of ERRP, a recently identified pan-**erbB antagonist** (Mol. Cancer Ther. 4: 435-442, 2005), were found to decrease with advancing age in patients with colorectal adenomas. We also observed that the expression of cyclooxygenase-2 (COX-2) increases with aging in patients with adenomas. in conclusion, there is a positive relationship between advancing age and polyp formation, This is associated with increased expression of EGFR and COX-2 and downregulation of ERRP.

L28 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN
2005:1154409 Document No. 143:420868 **ErbB Antagonists** and anti-ErbB2 antibodies and humanized derivatives or conjugates for treating pain or cancer-related pain. Agus, David B. (Agus, David B., USA). PCT Int. Appl. WO 2005099756 A2 20051027, 99 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-US11781 20050407. PRIORITY: US 2004-561076P 20040408.

AB The present application describes the use of **ErbB antagonists**, especially ErbB2 antibodies such as rhuMAb 2C4, for treating pain. The pain is selected from chronic pain, nociceptive pain, neuropathic pain, psychogenic pain, and cancer- or metastasis-related pain.

L28 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN
2001:868257 Document No. 136:11067 Gene detection assay for improving the likelihood of an effective response to **ErbB-antagonist** cancer therapy. Mass, Robert D. (Genentech, Inc., USA). PCT Int. Appl. WO 2001089566 A1 20011129, 40 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US16193 20010518. PRIORITY: US 2000-205754P 20000519.

AB The invention provides a method for more effective treatment of patients susceptible to or diagnosed with tumors overexpressing ErbB, as determined by a gene amplification assay, with an **ErbB antagonist.** Such method comprises administering a cancer-treating dose of the **ErbB antagonist**, preferably in addition to chemotherapeutic agents, to a subject in whose tumor cells ErbB has been found to be amplified e.g., by fluorescent in situ hybridization. **ErbB antagonists** described include an anti-HER2 antibody. Pharmaceutical packaging for providing the components for such treatment is also provided.

L28 ANSWER 4 OF 6 MEDLINE on STN DUPLICATE 1
2000406734. PubMed ID: 10918615. Evidence that Argos is an antagonistic ligand of the EGF receptor. Vinos J; Freeman M. (MRC Laboratory of Molecular Biology, Hills Road, Cambridge CB2 2QH, UK.) Oncogene, (2000 Jul 20) Vol. 19, No. 31, pp. 3560-2. Journal code: 8711562. ISSN: 0950-9232. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Argos, the inhibitor of the Drosophila epidermal growth factor (EGF) receptor, remains the only known extracellular inhibitor of this family of receptors in any organism. The functional domain of Argos includes an atypical EGF domain and it is not clear whether it binds to the EGF receptor or if it acts via a distinct receptor to reduce Egfr activity indirectly. Here we present two lines of evidence that strongly suggest that Argos directly interacts with the EGF receptor. First, Argos is unable to inhibit a chimeric receptor that contains an extracellular domain from an unrelated RTK, indicating the need for the EGF receptor extracellular domain. Second, Argos can inhibit the Drosophila EGF receptor even when expressed in human cells, implying that no other Drosophila protein is necessary for inhibition. We also report that Argos and the Drosophila activating ligand, Spitz, can influence mammalian RTK activation, albeit in a cell-type specific manner. This includes the first evidence that Argos can inhibit signalling in mammalian cells, raising the possibility of engineering an effective human EGF receptor/ **ErbB antagonist.** Oncogene (2000) 19, 3560 - 3562

L28 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN
1995:934129 Document No. 123:330042 Antagonists of EGF or TGF-α for treatment and prophylaxis of acne. Evenson, Alan; Gibson, Walter Thomas; Green, Martin Richard; Guy, Robert; Kealey, Terence George Evelyn (Unilever PLC, UK; Unilever NV). PCT Int. Appl. WO 9524896 A2 19950921, 22 pp. DESIGNATED STATES: W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TT, UA; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1995-EP877 19950308. PRIORITY: GB 1994-5046 19940315.

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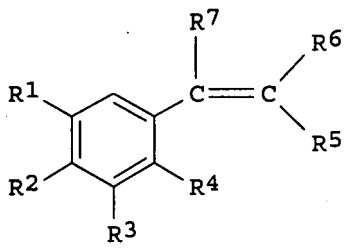

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AB Compns. comprising ≥1 antagonist of EGF, TGF-α, or EGF receptor function are useful in treating acne, spots, and pimples. Suitable EGF antagonists are tyrphostins [I; R1-R4 = H, OH, alkyl, NO2,

Cl, Br, F, CHO; R5, R6 = H, CN, CO2H, C(O)NH2, C(S)NH2; R7 = H, OH]. Thus, a lotion was prepared containing 3,4-dihydroxy-α-cyanocinnamamide (II) 0.001, EtOH 10, perfume, BHT 0.01, and H2O to 100 weight%. II prevented rupture of isolated human pilosebaceous gland ducts in the presence of EGF.

L28 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN
1994:409420 Document No. 121:9420 Schiff base-substituted phenols, process for their preparation and their use in the treatment of cell proliferation-associated diseases. Matusch, Rudolf; Czech, Joerg; Hunz, Manfred; Sedlacek, Hans Harald (Behringwerke AG, Germany). Eur. Pat. Appl. EP 586917 A1 19940316, 16 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE. (German). CODEN: EPXXDW. APPLICATION: EP 1993-112920 19930812. PRIORITY: DE 1992-4230262 19920910.

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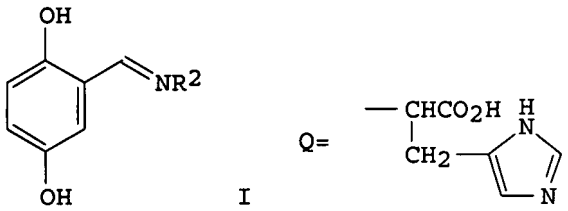

I

AB The title compds. [I; R2 = Me, Et, hexyl, iso-Pr, (un)substituted Ph, PhCH2, Q, amino acid residues, N-heterocyclo, etc.], useful in the treatment of cell proliferation diseases (e.g., psoriasis, tumors, etc.), are prepared by formation of the Schiff base of 2,5-dihydroxybenzaldehyde with an equimolar amount of the corresponding amine in anhydrous MeOH with removal of reaction water. Thus, 2,5-dihydroxybenzaldehyde was condensed with 1-amino-4-methylpiperazine, producing 2,5-dihydroxy-N-(4-methylpiperazino)benzaldimine (II), m.p. 250° in 65% theor. yields. II demonstrated IC50 for tyrosine kinase activity in the human tumor cell line A 431 (ATCC CRL 1555) of 0.56 μg/mL.

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=> s (brunetta p?/au or sliwkowski m?/au)
L29         604 (BRUNETTA P?/AU OR SLIWKOWSKI M?/AU)

=> s l29 and ErbB2
L30         174 L29 AND ERBB2

=> s l30 and antibod?
L31          93 L30 AND ANTIBOD?

=> s l31 and treat?
L32          32 L31 AND TREAT?

=> dup remove l32
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L33          15 DUP REMOVE L32 (17 DUPLICATES REMOVED)

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L33 ANSWER 1 OF 15 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
2006:551822 Document No.: PREV200600564736. **Treating** prostate cancer with anti-**ErbB2 antibodies.** Anonymous; **Sliwkowski, Mark X.** [Inventor]. San Carlos, CA USA. ASSIGNEE: Genentech Inc. Patent Info.: US 07041292 20060509. Official Gazette of the United States Patent and Trademark Office Patents, (MAY 9 2006) CODEN: OGUPE7. ISSN: 0098-1133. Language: English.

AB The present application discloses **treatment** of prostate cancer with anti-**ErbB2 antibodies.**

L33 ANSWER 2 OF 15 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
2006:288957 Document No.: PREV200600295933. Humanized anti-**ErbB2 antibodies** and **treatment** with anti-**ErbB2 antibodies. Sliwkowski, Mark** [Inventor]. San Carlos, CA USA. ASSIGNEE: Genentech, Inc.. Patent Info.: US 06949245 20050927. Official Gazette of the United States Patent and Trademark Office Patents, (SEP 27 2005)
CODEN: OGUPE7. ISSN: 0098-1133. Language: English.
AB The present application describes humanized anti-**ErbB2 antibodies** and methods for **treating** cancer with anti-**ErbB2 antibodies**, such as humanized anti-**ErbB2 antibodies.**

L33 ANSWER 3 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
2005:1314363 Document No. 144:57544 **Antibody** drug conjugates and uses for cancer therapy. Ebens, Allen J., Jr.; Jacobson, Frederic S.; Polakis, Paul; Schwall, Ralph H.; **Sliwkowski, Mark X.**; Spencer, Susan D. (Genentech, Inc., USA). PCT Int. Appl. WO 2005117986 A2 20051215, 110 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-US18829 20050531. PRIORITY: US 2004-576517P 20040601; US 2004-616098P 20041005.
AB The present invention relates to **antibody**-drug conjugate compds. with a formula of Ab-(L-D)p where 1 to 8 (p) maytansinoid drug moieties (D) are covalently linked by L to an **antibody** (Ab) which binds to an ErbB receptor, or which binds to one or more tumor-associated antigens or cell-surface receptors. These compds. may be used in methods of diagnosis or **treatment** of cancer, and other diseases and disorders.

L33 ANSWER 4 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
2004:467984 Document No. 141:22217 Therapy of non-malignant diseases or disorders with anti-**ErbB2 antibodies.** **Sliwkowski, Mark X.**; **Brunetta, Paul G.** (Genentech, Inc., USA). PCT Int. Appl. WO 2004048525 A2 20040610, 74 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US37367 20031121. PRIORITY: US 2002-428027P 20021121.
AB The authors disclose the preparation and biol. activity of murine and humanized **antibodies** to HER2. In one example, an anti-HER2 **antibody** is shown to inhibit heregulin-induced activation of Akt kinase and **erbB2** association with erbB3. The present application describes **treatment** of non-malignant indications, such as psoriasis, endometriosis, scleroderma, vascular diseases or disorders, respiratory disease, colon polyps or fibroadenoma, with anti-**ErbB2 antibodies** (e.g. rhuMAb 2C4).

L33 ANSWER 5 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
2004:59563 Document No. 140:122766 **Treatment** of cancer with anti-**ErbB2 antibodies.** Kelsey, Stephen M.; **Sliwkowski,**

Mark X. (Genentech, Inc., USA). U.S. Pat. Appl. Publ. US 2004013667 A1 20040122, 56 pp., Cont.-in-part of U.S. Ser. No. 268,501. (English). CODEN: USXXCO. APPLICATION: US 2003-608626 20030627. PRIORITY: US 1999-141316P 19990625; US 2000-602812 20000623; US 2002-268501 20021010.

AB The present application describes methods for **treating** cancer with anti-**ErbB2 antibodies**, such as anti-**ErbB2 antibodies** that block ligand activation of an ErbB receptor. Recombinant humanized monoclonal **antibody** 2C4 was effective in inhibiting breast cancer tumor growth in mice with MCF7 xenografts.

L33 ANSWER 6 OF 15 MEDLINE on STN DUPLICATE 1

2004585637. PubMed ID: 15385631. Endocytosis and sorting of **ErbB2** and the site of action of cancer therapeutics trastuzumab and geldanamycin. Austin Cary D; De Maziere Ann M; Pisacane Paul I; van Dijk Suzanne M; Eigenbrot Charles; **Sliwkowski Mark X**; Klumperman Judith; Scheller Richard H. (Genentech, Inc., South San Francisco, CA 94080, USA.) Molecular biology of the cell, (2004 Dec) Vol. 15, No. 12, pp. 5268-82. Electronic Publication: 2004-09-22. Journal code: 9201390. ISSN: 1059-1524. Pub. country: United States. Language: English.

AB **ErbB2** is a transmembrane tyrosine kinase whose surface overexpression is linked to tumorigenesis and poor prognosis in breast cancer patients. Two models have emerged that account for the high surface distribution of **ErbB2.** In one model, the surface pool is dynamic and governed by a balance between endocytosis and recycling, whereas in the other it is retained, static, and excluded from endocytosis. These models have contrasting implications for how **ErbB2** exerts its biological function and how cancer therapies might down-regulate surface **ErbB2**, such as the **antibody** trastuzumab (Herceptin) or the Hsp90 inhibitor geldanamycin. Little is known, however, about how these **treatments** affect **ErbB2** endocytic trafficking. To investigate this issue, we examined breast carcinoma cells by immunofluorescence and quantitative immunoelectron microscopy and developed imaging and trafficking kinetics assays using cell surface fluorescence quenching. Surprisingly, trastuzumab does not influence **ErbB2** distribution but instead recycles passively with internalized **ErbB2.** By contrast, geldanamycin down-regulates surface **ErbB2** through improved degradative sorting in endosomes exclusively rather than through increased endocytosis. These results reveal substantial dynamism in the surface **ErbB2** pool and clearly demonstrate the significance of endosomal sorting in the maintenance of **ErbB2** surface distribution, a critical feature of its biological function.

L33 ANSWER 7 OF 15 MEDLINE on STN DUPLICATE 2

2004165913. PubMed ID: 15059917. Blockade of epidermal growth factor- or heregulin-dependent **ErbB2** activation with the anti-**ErbB2** monoclonal **antibody** 2C4 has divergent downstream signaling and growth effects. Jackson James G; St Clair Patricia; **Sliwkowski Mark X**; Brattain Michael G. (Department of Surgery, University of Texas Health Science Center, San Antonio, Texas, USA.) Cancer research, (2004 Apr 1) Vol. 64, No. 7, pp. 2601-9. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB Due to heterodimerization and a variety of stimulating ligands, the ErbB receptor system is both diverse and flexible, which proves particularly advantageous to the aberrant signaling of cancer cells. However, specific mechanisms of how a particular receptor contributes to generating the flexibility that leads to aberrant growth regulation have not been well described. We compared the utilization of **ErbB2** in response to epidermal growth factor (EGF) and heregulin stimulation in colon carcinoma cells. Anti-**ErbB2** monoclonal **antibody** 2C4 blocked heregulin-stimulated phosphorylation of **ErbB2** and ErbB3; activation of mitogen-activated protein kinase (MAPK), phosphatidylinositol 3'-kinase (PI3K), and Akt; proliferation; and anchorage-independent growth. 2C4 blocked EGF-mediated phosphorylation of **ErbB2** and inhibited PI3K/Akt and anchorage-independent growth but

did not affect ErbB1 or MAPK. Immunoprecipitations showed that ErbB3 and Grb2-associated binder (Gab) 1 were phosphorylated and associated with PI3K activity after heregulin **treatment** and that Gab1 and Gab2, but not ErbB3, were phosphorylated and associated with PI3K activity after EGF **treatment.** These data show that monoclonal **antibody** 2C4 inhibited all aspects of heregulin signaling as well as anchorage-independent and monolayer growth. Furthermore, we identify **ErbB2** as a critical component of EGF signaling to the Gab1/Gab2-PI3K-Akt pathway and anchorage-independent growth, but EGF stimulation of MAPK and monolayer growth can occur efficiently without the contribution of **ErbB2.**

L33 ANSWER 8 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN

2003:355612 Document No. 138:362649 **Treatment** of cancer with anti-**ErbB2 antibodies. Sliwkowski, Mark X.** (Genentech, Inc., USA). U.S. Pat. Appl. Publ. US 2003086924 A1 20030508, 56 pp., Cont.-in-part of U.S. Ser. No. 602,812. (English). CODEN: USXXCO. APPLICATION: US 2002-268501 20021010. PRIORITY: US 1999-141316P 19990625; US 2000-602812 20000623.

AB The present application describes methods for **treating** cancer with anti-**ErbB2 antibodies**, such as anti-**ErbB2 antibodies** that block ligand activation of an ErbB receptor. Recombinant humanized monoclonal **antibody** 2C4 was effective in inhibiting breast cancer tumor growth in MCF7 xenografts.

L33 ANSWER 9 OF 15 MEDLINE on STN

2002445205. PubMed ID: 12204533. Targeting ligand-activated **ErbB2** signaling inhibits breast and prostate tumor growth. Agus David B; Akita Robert W; Fox William D; Lewis Gail D; Higgins Brian; Pisacane Paul I; Lofgren Julie A; Tindell Charles; Evans Douglas P; Maiese Krista; Scher Howard I; **Sliwkowski Mark X.** (Cedars-Sinai Prostate Cancer Center, Los Angeles, California 90048, USA.) Cancer cell, (2002 Aug) Vol. 2, No. 2, pp. 127-37. Journal code: 101130617. ISSN: 1535-6108. Pub. country: United States. Language: English.

AB **ErbB2** is a ligand-less member of the ErbB receptor family that functions as a coreceptor with EGFR, ErbB3, and ErbB4. Here, we describe an approach to target **ErbB2**'s role as a coreceptor using a monoclonal **antibody**, 2C4, which sterically hinders **ErbB2**'s recruitment into ErbB ligand complexes. Inhibition of ligand-dependent **ErbB2** signaling by 2C4 occurs in both low- and high-**ErbB2**-expressing systems. Since the ErbB3 receptor contains an inactive tyrosine kinase domain, 2C4 is very effective in blocking heregulin-mediated ErbB3-**ErbB2** signaling. We demonstrate that the in vitro and in vivo growth of several breast and prostate tumor models is inhibited by 2C4 **treatment.**

L33 ANSWER 10 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN

2002:11123 Document No. 136:64172 Chimeric ErbB heteromultimer adhesins as neuregulin antagonists and agonists, and therapeutic use thereof. Fitzpatrick, Vincent Danial; **Sliwkowski, Mark**; Vandlen, Richard L. (Genentech, Inc., USA). U.S. Pat. Appl. Publ. US 2002002276 A1 20020103, 32 pp., Cont. of U.S. Ser. No. 21,233, abandoned. (English). CODEN: USXXCO. APPLICATION: US 2001-912942 20010725. PRIORITY: US 1997-37537P 19970210; US 1998-21233 19980210.

AB Chimeric heteromultimer adhesins that bind the ligand of natural heteromultimeric receptors, and uses therefor, are disclosed. The chimeric mols. of the heteromultimer adhesins comprise an extracellular domain of a heteromultimeric receptor monomer and a multimerization domain for the stable interaction of the chimeric mols. in the adhesin. Specifically disclosed are heteromultimeric adhesins comprising the extracellular domains of **ErbB2** and ErbB3 or **ErbB2** and ErbB4. The chimeric ErbB heteromultimer adhesins of the invention are useful as competitive antagonists or agonists of a neuregulin for the **treatment** of diseases, e.g. inflammation and cancer.

L33 ANSWER 11 OF 15 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN DUPLICATE 3

2005334985 EMBASE Targeting ligand-activated **ErbB2** signaling inhibits breast and prostate tumor growth. Agus D.B.; Akita R.W.; Fox W.D.; Lewis G.D.; Higgins B.; Pisacane P.I.; Lofgren J.A.; Tindell C.; Evans D.P.; Maiese K.; Scher H.I.; **Sliwkowski M.X.**. M.X. Sliwkowski, Department of Molecular Oncology, Genentech, South San Francisco, CA 94080, United States. marks@gene.com. Cancer Cell Vol. 2, No. 2, pp. 127-137 2002.
Refs: 74.
ISSN: 1535-6108. CODEN: CCAECI
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20050825. Last Updated on STN: 20050825

AB **ErbB2** is a ligand-less member of the ErbB receptor family that functions as a coreceptor with EGFR, ErbB3, and ErbB4. Here, we describe an approach to target **ErbB2**'s role as a coreceptor using a monoclonal **antibody**, 2C4, which sterically hinders **ErbB2** 's recruitment into ErbB ligand complexes. Inhibition of ligand-dependent **ErbB2** signaling by 2C4 occurs in both low- and high-**ErbB2** -expressing systems. Since the ErbB3 receptor contains an inactive tyrosine kinase domain, 2C4 is very effective in blocking heregulin-mediated ErbB3-**ErbB2** signaling. We demonstrate that the in vitro and in vivo growth of several breast and prostate tumor models is inhibited by 2C4 **treatment.** Copyright .COPYRGT. 2002 Cell Press.

L33 ANSWER 12 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN

2001:12297 Document No. 134:99574 **Treating** prostate cancer with anti-**ErbB2 antibodies.** Agus, David B.; Scher, Howard I.; **Sliwkowski, Mark X.** (Genentech, Inc., USA; Sloan-Kettering Institute for Cancer Research). PCT Int. Appl. WO 2001000238 A1 20010104, 93 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US17423 20000623. PRIORITY: US 1999-PV141315 19990625.

AB The present application discloses **treatment** of prostate cancer with anti-**ErbB2 antibodies.** These **antibodies** are combined with chemotherapeutic agent, cytokine, antiangiogenic agent, EGFR-targeted drug, antiandrogen, anthracycline antibiotic, etc. for **treating** androgen-(in)dependent prostate cancer.

L33 ANSWER 13 OF 15 MEDLINE on STN DUPLICATE 4

2001184971. PubMed ID: 11252954. Untangling the ErbB signalling network. Yarden Y; **Sliwkowski M X.** (Department of Biological Regulation, Weizmann Institute of Science, Rehovot 76100, Israel.. yosef.yarden@weizmann.ac.il) . Nature reviews. Molecular cell biology, (2001 Feb) Vol. 2, No. 2, pp. 127-37. Ref: 112. Journal code: 100962782. ISSN: 1471-0072. Pub. country: England: United Kingdom. Language: English.

AB When epidermal growth factor and its relatives bind the ErbB family of receptors, they trigger a rich network of signalling pathways, culminating in responses ranging from cell division to death, motility to adhesion. The network is often dysregulated in cancer and lends credence to the mantra that molecular understanding yields clinical benefit: over 25,000 women with breast cancer have now been **treated** with trastuzumab (Herceptin), a recombinant **antibody** designed to block the receptor **ErbB2.** Likewise, small-molecule enzyme inhibitors and monoclonal **antibodies** to ErbB1 are in advanced phases of clinical testing. What can this pathway teach us about translating basic science into clinical use?

L33 ANSWER 14 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
1999:269587 Document No. 131:67755 Inhibitory effects of combinations of HER-2/neu **antibody** and chemotherapeutic agents used for **treatment** of human breast cancers. Pegram, Mark; Hsu, Sheree; Lewis, Gail; Pietras, Richard; Beryt, Malgorzata; **Sliwkowski, Mark**; Coombs, Daniel; Baly, Deborah; Kabbinavar, Fairooz; Slamon, Dennis (Division of Hematology-Oncology, UCLA School of Medicine, Los Angeles, CA, 90095, USA). Oncogene, 18(13), 2241-2251 (English) 1999. CODEN: ONCNES. ISSN: 0950-9232. Publisher: Stockton Press.

AB Previous studies have demonstrated a synergistic interaction between rhuMAb HER2 and the cytotoxic drug cisplatin in human breast and ovarian cancer cells. To define the nature of the interaction between rhuMAb HER2 and other classes of cytotoxic drugs, the authors applied multiple drug effect/combination index (CI) isobologram anal. to a variety of chemotherapeutic drug/rhuMAb HER2 combinations in vitro. Synergistic interactions at clin. relevant drug concns. were observed for rhuMAb HER2 in combination with cisplatin (CI = 0.48, P = 0.003), thiotepa (CI = 0.67, P = 0.0008), and etoposide (CI = 0.54, P = 0.0003). Additive cytotoxic effects were observed with rhuMAb HER2 plus doxorubicin (CI = 1.16, P = 0.13), paclitaxel (CI = 0.91, P = 0.21), methotrexate (CI = 1.15, P = 0.28), and vinblastine (CI = 1.09, P = 0.26). One drug, 5-fluorouracil, was found to be antagonistic with rhuMAb HER2 in vitro (CI = 2.87, P = 0.0001). In vivo drug/rhuMAb HER2 studies were conducted with HER-2/neu-transfected, MCF7 human breast cancer xenografts in athymic mice. Combinations of rhuMAb HER2 plus cyclophosphamide, doxorubicin, paclitaxel, methotrexate, etoposide, and vinblastine in vivo resulted in a significant reduction in xenograft volume compared to chemotherapy alone ($P<0.05$). Xenografts **treated** with rhuMAb HER2 plus 5-fluorouracil were not significantly different from 5-fluorouracil alone controls consistent with the subadditive effects observed with this combination in vitro. The synergistic interaction of rhuMAb HER2 with alkylating agents, platinum analogs and topoisomerase II inhibitors, as well as the additive interaction with taxanes, anthracyclines and some antimetabolites in HER-2/neu-overexpressing breast cancer cells demonstrates that these are rational combinations to test in human clin. trails.

L33 ANSWER 15 OF 15 MEDLINE on STN DUPLICATE 5
97472144. PubMed ID: 9333014. Gamma-heregulin: a novel heregulin isoform that is an autocrine growth factor for the human breast cancer cell line, MDA-MB-175. Schaefer G; Fitzpatrick V D; **Sliwkowski M X.** (Genentech, Inc., South San Francisco, California 94080, USA.) Oncogene, (1997 Sep 18) Vol. 15, No. 12, pp. 1385-94. Journal code: 8711562. ISSN: 0950-9232. Pub. country: ENGLAND: United Kingdom. Language: English.

AB A novel neuregulin isoform, termed gamma-HRG, was cloned and characterized from the human breast cancer cell line, MDA-MB-175. As observed with other neuregulins, gamma-HRG, is a product of alternative mRNA splicing of the neuregulin gene. Gamma-HRG contains the EGF-like and immunoglobulin-like domains that are commonly found in other family members, but lacks a transmembrane and cytoplasmic region. The new isoform possesses a unique N-terminal region that includes a hydrophobic domain that may function as a secretion signal. A purified recombinant version of gamma-HRG competes for binding to soluble ErbB3- and ErbB4-IgG fusion proteins with affinities similar to those observed for rHRGbeta1(177-244). Gamma-HRG has a wide distribution in mesenchymal or neuronal tissues but in contrast to other neuregulins, it is not present in breast, lung, liver and small intestine. Expression of gamma-HRG with its cognate receptors, ErbB3 and **ErbB2** suggested that the growth of the MDA-MB-175 cell line might be a result of the autocrine stimulation of a growth factor signaling pathway. **Treatment** of MDA-MB-175 cells with an anti-**ErbB2** monoclonal **antibody** that interferes with the ligand-dependent formation of **ErbB2**-ErbB3 heterodimer complexes shows a strong growth inhibitory effect on this cell line. Moreover, incubation with a receptor-IgG fusion protein that neutralizes secreted gamma-HRG, also inhibits cell growth. These data

suggest that the secretion of gamma-HRG by MDA-MB-175 cells leads to the formation of a constitutively active receptor complex and stimulates the growth of these cells in an autocrine manner.

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